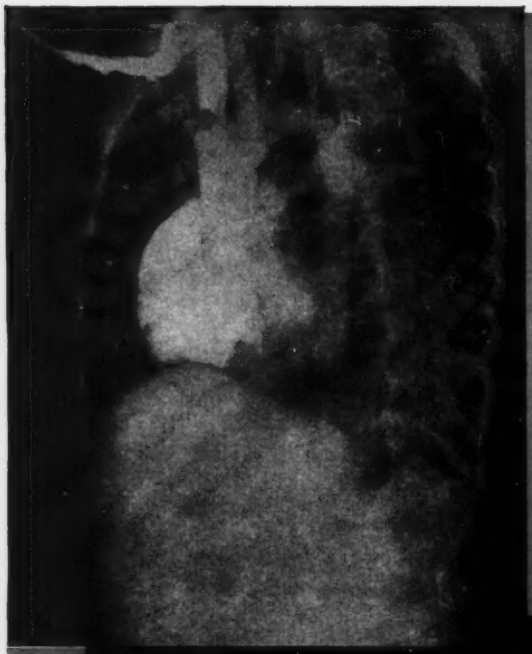
DECEMBER 1954
VOL. X NO. 6

Circulation

JOURNAL of the AMERICAN HEART ASSOCIATION

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

Published by Grune & Stratton, Inc.



Angiocardiography

Angiocardiography with Diodrast 70 per cent solution — whether by means of intravenous injection or by the technic of intracardiac catheterization — is now a well standardized and often immensely helpful procedure.

Diodrast®

Concentrated Solution 70%

Ampuls of 20 cc. and 50 cc.

Specific instances in which it may be of unsurpassed diagnostic value are congenital lesions such as patent ductus arteriosus, tetralogy of Fallot, coarctation of the aorta, patent foramen ovale, dextrocardia, etc.; aneurysms, mediastinal lesions and chronic pericarditis.

Winthrop-Stearns INC.

NEW YORK 18, N. Y. WINDSOR, ONT.

Diodrast, trademark reg. U. S. & Canada, brand of iodopyracet

Circulation
A Journal of the American Heart Association

DECEMBER 1954
VOL. X NO. 6

Pathology of the Pulmonary Vascular Tree

IV. Structural Changes in the Pulmonary Vessels in Chronic Left Ventricular Failure

By ROGER C. SMITH, M.D., HOWARD B. BURCHELL, M.D., AND JESSE E. EDWARDS, M.D.

Previous studies in this series demonstrated structural changes in the pulmonary vascular bed as the result of mitral valvular disease and other cardiac disorders. The present study demonstrates changes in the lungs as the result of chronic left ventricular failure; these changes were like those produced by mitral stenosis. The most pronounced disturbance was medial hypertrophy. The exact mechanism is not known, but it probably is related to increased pulmonary venous pressure.

WITH the increased knowledge of cardiovascular physiology imparted by means of cardiac catheterization, parallel interest has been manifested in the structural changes that occur in the pulmonary vascular tree under various conditions, especially those associated with increased pulmonary arterial pressure. In earlier studies it has been demonstrated that in mitral stenosis[1, 2] and in mitral insufficiency,[3] as well as in other cardiac disorders, structural changes may occur in the pulmonary vascular bed.[4] When cardiac disease creates an impediment to pulmonary venous outflow, the pulmonary vascular changes are primarily those of medial hypertrophy of the muscular arteries.

Chronic left ventricular failure, like mitral stenosis or mitral insufficiency, is associated with impaired pulmonary venous outflow and increased pulmonary "capillary" and arterial pressures.[5-9] The thought that this functional derangement might be associated with demonstrable structural changes in the pulmonary vascular tree led to the present study on histologic changes in the pulmonary vessels in cases of chronic left ventricular failure.

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Abridgment of thesis submitted by Dr. Smith to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

MATERIAL AND METHODS

Initially, it was desired to have three groups as follows: Group 1 included cases in which chronic left ventricular failure had resulted from calcific aortic stenosis or systemic hypertension. Group 2 included cases of calcific aortic stenosis or systemic hypertension without left ventricular failure. Group 3 included cases in which cardiovascular disease was absent. Later, a fourth group was studied; this group was made up of cases in which mitral stenosis was present.

Emphysema[10] and other forms of pulmonary disease and aging may be associated with structural abnormalities in the pulmonary vascular tree. In order to exclude such cases as far as possible, records of patients 60 years of age or more were not included. Selection of cases for study included histologic examination of pulmonary tissue from persons potentially to be included in one group or another without knowledge at the time of this examination into which group the case would be placed if emphysema and other pulmonary diseases were not present. If pulmonary disease was present the case was not included.

After such elimination, the composition of the three groups was as follows: Group 1 was made up

of 24 cases, in each of which chronic left ventricular failure had been present. The criteria for left ventricular failure were basically those given by White.[11] The most constant feature was recurrent paroxysmal nocturnal dyspnea. Among the 24 cases in this group, six represented calcific aortic stenosis and 18 represented systemic hypertension. Healed myocardial infarction was also present in some of the cases in this group. Twelve of the patients were men and 12 were women; the ages ranged from 36 to 59 years, with a median age of 49 years. The mean cardiac weight in this group was 600 Gm., with a range of 420 to 920 Gm. In 17 of the cases, the cardiac weight was 600 Gm. or more. The duration of left ventricular failure varied from about 2 months to about 10 years; in the majority of cases, this functional disturbance had been present from about eight months to two years.

Group 2 also was composed of 24 cases; calcific aortic stenosis was present in two and systemic hypertension had been present in 22. None of these patients had presented clinical evidence of left ventricular failure. Nine were women and 15 were men. Their ages varied from 40 to 58 years, with a median age of 52 years.

Group 3 comprised 20 cases. No clinical or pathologic evidence of cardiac disease was present in any of these cases. Many of the patients in this group had died of cerebral neoplasms. Six were men and 14 were women. Their ages ranged from 39 to 58 years, with a median age of 46 years.

From each person included in the study two sections of lung, chosen at random as to lobes, were stained by Verhoeff's method for elastic tissue and counterstained by van Gieson's method for connective tissue. The sections were then examined histologically according to the methods to be described.

Definition of Terms

Since potential lack of uniformity exists regarding terminology, it is pertinent to designate the types of pulmonary vessels to which reference will be made and to describe their basic structures. In general the terminology to be employed is similar to that of Brenner.[12] The classes of vessels studied were muscular arteries, arterioles and veins.

Muscular arteries vary in diameter from 1 mm. to somewhat less than 0.1 mm. These vessels are further divided into large muscular arteries and small muscular arteries (fig. 1*a*, *b* and *c*). The large muscular arteries are associated with a small bronchus and arise by branching from elastic arteries. The small muscular arteries arise as right-angled branches from the large muscular arteries. Whether large or small, the muscular arteries have a thin intima composed of lining endothelium and a small amount of collagenous tissue resting on the internal elastic membrane. The media is composed of a well-defined band of muscle fibers arranged in a circular fashion lying between the internal and external elastic membranes. In the large muscular arteries occasional elastic fibers are interspersed along the muscle fibers of the media. The adventitia is composed of dense collagenous connective tissue.

The arterioles are designated as those vessels arising from the small muscular arteries and lying between the small muscular artery and the capillary bed (fig. 1*d* and *e*). The structure of this class of vessel is characterized by an endothelial lining and a small amount of connective tissue, including an elastic membrane, lying in a subendothelial position. The elastic membrane was continuous with the internal elastic lamina of the parent muscular artery. Although muscle fibers cannot be identified with certainty in the wall of the arteriole, at the same time their absence cannot be categorically denied.

The veins in this study were divided into two groups, large and small. The structure of the small veins, or venules, is like that of the arterioles (fig. 1*f*). In general venules are wider than arterioles, but it is difficult to distinguish these vessels from each other in random sections of lung. While attempts were made to classify the changes in arterioles and in venules, it is to be admitted that the distinction between these two classes of vessels was probably not always accurate. The large veins present an intimal layer that, as in the arteries, is thin. The media contains well-defined muscle bundles that are irregularly arranged and separated by connective tissue, mainly collagenous. The adventitia is composed of thick collagenous bundles, among which are varying numbers of elastic fibers. In contrast to the muscular arteries, in which the media is distinctly demarcated from the adventitia by the external elastic membrane, the large veins exhibit a poorly defined transition between these two layers.

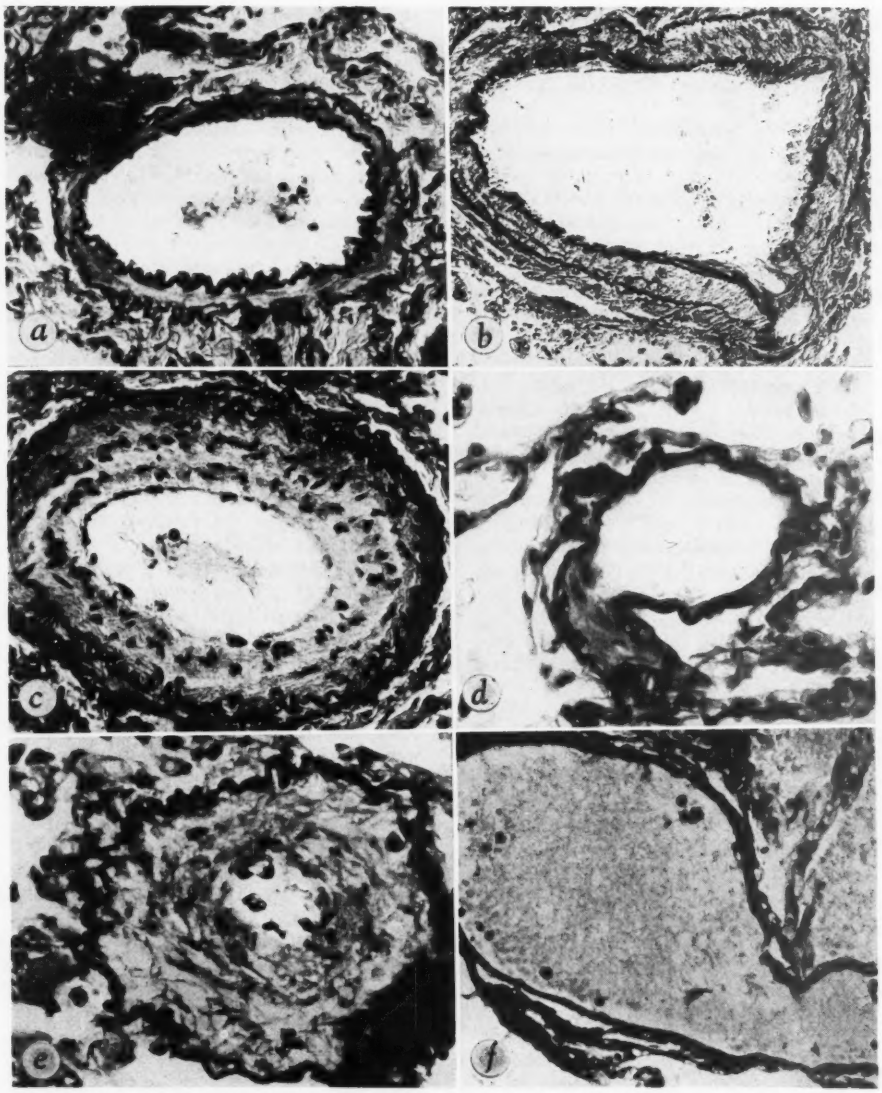


FIG. 1. Pulmonary vessels. All sections were stained by Verhoeff's method for elastic tissue and counterstained by van Gieson's method for connective tissue. *a*. Normal small muscular artery (× 350). *b*. Large muscular artery with medial hypertrophy, grade 3 (× 115). *c*. Small muscular artery with intimal hyperplasia and fibrous proliferation grade 3 (× 330). *d*. Normal arteriole (× 430). *e*. Arteriole with intimal proliferation grade 4 (× 430). *f*. Normal small vein (× 245).

GRADING OF VASCULAR CHANGES AND DETERMINATION OF INDEX OF CHANGE

An attempt was made to approach a quantitative measurement of alteration in several elements of the pulmonary vascular tree. This was done by developing a method of determining an "index of change." The units of the pulmonary vascular tree for which indexes of change were determined included the media and the intima of both large and small muscular arteries, as well as the intima of the arterioles, venules and the large veins.

The index of change was derived from (1) the

evaluation of the greatest degree of change, termed the "grade of severity," that was present in the vascular unit under study and (2) an estimation as to the extent of this change, termed the "grade of distribution."

Grade of Severity. The grade of severity with regard to the media of the muscular arteries was indicated on a basis of 0 to 4. A grade of 0 represented no discernible change; grade 1 indicated an increase in thickness of the media up to 100 per cent more than normal; grade 2 indicated thickening up to 200 per cent above normal; grade 3 indicated thickening up to 300 per cent and grade 4 represented thickening of more than 300 per cent of normal.

The grade of severity with regard to the intimal change, which consisted of fibrous thickening, was recorded on the basis of the greatest degree of luminal narrowing that the change in intimal tissue had caused. Intimal thickening of grade 0 was recorded when the intima was of normal thickness. Intimal changes considered as grade 1 were represented by thickening of the intima beyond the normal range but which produced narrowing of the luminal diameter of less than 25 per cent. Narrowing of the lumen ranging from 25 to 49 per cent of the diameter was considered as grade 2 intimal fibrous thickening; luminal narrowing ranging from 50 to 74 per cent represented grade 3, whereas grade 4 intimal fibrous thickening represented luminal narrowing of 75 per cent or more. The same method was used for the intimas of the muscular arteries, arterioles and venules. The grade of severity for the intima of the large veins was determined from the ratio (expressed as per cent) of the intima to the total thickness of the wall of the vein. If the intima was of normal thickness, the changes were graded as 0. If intimal thickening amounted to as much as 25 per cent of the total thickness of the wall, it was graded 1; thickening up to 50 per cent was graded 2, thickening up to 75 per cent was graded 3 and that up to 100 per cent was graded 4.

Grade of Distribution. A grade of distribution was recorded for the severest grade of change in each element. If the greatest degree of change present was observed in up to a fourth of the vascular elements under scrutiny, the grade of distribution was 1; it was grade 2 when about half the units were so involved; grade 3 indicated that about three fourths of the vascular units were so affected, whereas grade 4 indicated maximal changes in essentially all such elements.

Index of Change. As indicated previously, the index of change for each vascular unit in each section studied was determined by means of the grade of severity and the grade of distribution. This was done by obtaining the product of these two grades. To determine the index of change for the particular vascular unit in each case, the index of change for each of the two sections was determined and the two indexes were averaged.

The following is an example of the method used in determining the index of change for one vascular element. The greatest degree of intimal change among the large muscular arteries represented a grade of severity of 3. The distribution of this greatest degree of change involved about half of the large muscular arteries, yielding a grade of distribution of 2. The product of these two grades (3 times 2) gives an index of change of 6 for the intima in the large muscular arteries of that section. If the second section in the case being studied gave an index of change for the intima of the large muscular arteries of 8, the average of index of change for this vascular element would be 7, which would be considered the index of change for the intima of the large muscular arteries in that particular case.

Averages for the index of change of each vascular element studied were made for each of the groups of cases studied. After the findings in these three groups were compared with each other, it was of interest to compare them with what might be found in mitral stenosis.

Accordingly, as previously mentioned, the records in 10 cases of established rheumatic mitral stenosis in which the patients had died of this valvular disease were collected to represent group 4. Five of the patients were women and five were men. The ages varied from 35 to 54 years, the median age being 42 years. The pulmonary tissue in these cases was examined by the same methods that were applied to the other groups.

As already indicated, at the time of examination of the histologic sections in groups 1, 2 and 3, it was not known in which of these groups the individual cases belonged. It was only after the indexes of change for the various vascular elements were determined in all the cases in these three groups that the key was exposed and the cases arranged according to their proper groups. However, when the sections in group 4 were examined, it was known that they were from cases of mitral stenosis.

Results

The general results of this study are summarized in table 1.

Group 1 (Chronic Left Ventricular Failure)

Large Muscular Arteries. Large muscular arteries were found in the sections in 21 of the 24 cases in which clinical evidence of chronic left ventricular failure had been present. The average index of change of the media of these arteries in this group was 5.0 (range, 0 to 12).

TABLE 1.—*Average Indexes of Change in the Pulmonary Vascular Tree*

Condition	Large muscular arteries		Small muscular arteries		Arterioles*	Small veins*	Large veins*
	Media	Intima	Media	Intima			
Calcific aortic stenosis or systemic hypertension with chronic left ventricular failure (group 1)	5.0 (0–12)†	2.1 (0–8)	2.7 (0–9)	3.1 (0–10.5)	4.4 (1–10.5)	4.9 (2–14)	5.2 (0–16)
Calcific aortic stenosis or systemic hypertension without left ventricular failure (group 2)	0.7 (0–8)	0.8 (0–4)	0.5 (0–4)	1.5 (0–6.5)	1.9 (0–9)	2.9 (0–8)	1.9 (0–8)
No evidence of cardiovascular disease (group 3)	0.2 (0–2)	0.25 (0–2)	0.1 (0–1.5)	1.0 (0–4)	2.2 (0–5.5)	3.0 (0–6)	1.9 (0–8)
Mitral stenosis (group 4)	8.8 (0–16)	1.2 (0–4)	3.6 (0–7)	2.5 (0–8)	4.5 (2–8)	4.9 (2.5–8)	5.4 (4–12)

* Only intimal changes graded. † Range of indexes of change.

No changes (grade 0) were found in the media of the large muscular arteries in five cases; in seven, the indexes of change varied from 7.0 to 12.0, whereas the indexes ranged from 2.0 to 6.5 in the remaining nine cases. The average index of change in the intimal coat of the large muscular arteries in this group was 2.1 (range, 0 to 8.0). In nine of the cases no changes in the intimal coat were found (grade 0); in one case the index was 8.0, and in the remaining 11 the indexes ranged from 1.0 to 6.0.

Small Muscular Arteries. Small muscular arteries were present in the sections studied in all 24 cases in group 1. For the group the average index of change of the media of these small muscular arteries was 2.7 (range, 0 to 9.0). No change in the medial coat (grade 0) was present in 5; in the remaining 19 cases, 3 had indexes of change in the medial coat that varied from 7.0 to 9.0, whereas 16 had indexes that varied from 0.5 to 5.0. The average index of change in the intima of these small muscular arteries was 3.1 (range, 0 to 10.5). The intimal changes were classified as grade 0 in 8 cases; in the remaining 16 cases, 5 had indexes ranging from 7.5 to 10.5 and 11 had indexes varying from 1.0 to 6.0.

Arterioles. The average index of change of the intima of the arterioles in group 1 was 4.4 (range, 1.0 to 10.5); the indexes ranged from 7.5 to 10.5 in 4 cases and from 1 to 6 in 20 cases.

Small Veins. The average index of change of the intima of the small veins in group 1 was 4.9 (range, 2.0 to 14.0); the indices varied from 7.0 to 14.0 in 6 cases and from 2.0 to 6.0 in 18 cases.

Large Veins. Large veins were present in the sections in 19 of the cases in group 1. The average index of change of the intima of these large veins was 5.2 (range, 0 to 16.0). No intimal changes were found in 1 case; in the remaining 18 cases, 5 had indexes that varied from 8.0 to 16.0, whereas 13 had indexes that ranged from 2.0 to 6.0.

Comparison of Degree of Change with Duration of Left Ventricular Failure and with Underlying Disease. When the duration of left ventricular failure, as determined from the clinical history, was plotted against the degree of change, as expressed by the summation of the indexes of medial and intimal changes in the large and small muscular arteries, the resultant scattergram showed no obvious correlation with the duration of left ventricular failure. Likewise, no clear correlation was seen when the duration of left ventricular failure was plotted against the summation of the indexes of change found in all the elements graded in each particular case. Considerable difference was noted in these indexes when the cases were separated into those in which calcific aortic stenosis was present and those in which systemic hypertension was present. In general, a greater index of change was associated with calcific aortic stenosis than with systemic hypertension in the cases studied (table 2).

TABLE 2.—*Average Indexes of Change in the Pulmonary Vascular Tree in Chronic Left Ventricular Failure and in Mitral Stenosis*

Condition	Large muscular arteries		Small muscular arteries		Arterioles*	Small veins*	Large veins*
	Media	Intima	Media	Intima			
Calcific aortic stenosis with left ventricular failure (subdivision of group 1)	7.7 (4–12)†	1.7 (0–6)	4.7 (3–7.5)	4.5 (1–10.5)	5.6 (1–10)	8.0 (2–14)	9.4 (4–16)
Hypertensive cardiovascular disease with left ventricular failure (subdivision of group 1)	4.0 (0–12)	2.3 (0–8)	2.0 (0–9)	2.5 (0–8)	3.8 (1–10.5)	3.7 (2–4)	3.7 (0–12)
Mitral stenosis (group 4)	8.8 (0–16)	1.2 (0–4)	3.6 (0–7)	2.5 (0–8)	4.5 (2–8)	4.9 (2.5–8)	5.4 (4–12)

* Only initimal changes graded. † Range of indexes of change.

Group 2 (Calcific Aortic Stenosis or Systemic Hypertension without Left Ventricular Failure)

Large Muscular Arteries. Sections in 22 of the cases in group 2 contained large pulmonary muscular arteries. The average index of change of the media of these large muscular arteries was 0.7 (range, 0 to 8.0). In 16 cases, the index of change was classified as 0; in 1 case the index was 8.0, and in the remaining 5 cases the indexes ranged from 0.5 to 4.0. The average index of change of the intima was 0.8 (range, 0 to 4.0); in 16 cases the indexes were 0, whereas in 6 cases they ranged from 2.0 to 4.0.

Small Muscular Arteries. All the sections in this group contained small muscular arteries. The average index of change of the media of these small muscular arteries was 0.5 (range, 0 to 4.0). No change was noted in 18 cases, whereas the indexes ranged from 0.5 to 4.0 in 6 cases. The average index of change of the intima of these small muscular arteries for the entire group was 1.5 (range, 0 to 6.5). The intimal changes in 11 cases were classified as 0; in the remaining 13 cases, the indexes ranged from 1.0 to 6.5.

Arterioles. The average index of change of the intima of the arterioles in the 24 cases in this group was 1.9 (range, 0 to 9.0). In 9 cases, the changes were classified as 0; in 2 cases, the indexes were 6.5 and 9.0, whereas the remaining 13 had indexes that ranged from 1.0 to 4.0.

Small Veins. The average index of change of the intima of the small veins was 2.9 (range, 0 to 8.0). No change was noted in 4 cases; 1 case had an index of 8.0, and the remaining 19 showed indexes that ranged from 2.0 to 4.0.

Large Veins. Large veins were found in sections in 23 cases in this group. The average index of change of the intima of these large veins was 1.9 (range, 0 to 8.0). In 11 of the cases the intimal change was classified as 0; in 1 case the index was 8.0, and the remaining 11 cases had indexes that ranged from 2.0 to 6.0.

Group 3 (Normal Controls)

Large Muscular Arteries. The average index of change of the media of the large muscular arteries in this group was 0.2 (range, 0 to 2.0); the average index of change of the intima was 0.25 (range, 0 to 2.0).

Small Muscular Arteries. The average index of change of the media in the small muscular arteries was 0.1. In 19 of the cases, the medial changes were classified as 0; in the remaining case, the index was 1.5. The average index of change of the intima was 1.0 (range, 0 to 4.0).

Arterioles. The average index of change of the intima of the arterioles was 2.2 (range, 0 to 5.5).

Small Veins. The average index of change of the intima of the small veins was 3.0 (range, 0 to 6.0).

Large Veins. The average index of change of the intima of the large veins was 1.9 (range, 0 to 8.0). No intimal changes were noted in 10 cases; in 1 case the index was 8.0, and in the remaining 9 cases the indexes ranged from 2.0 to 4.0.

Group 4 (Mitral Stenosis)

The average indexes of change of the various pulmonary vascular elements in the 10 cases of mitral stenosis are given in table 1.

Comment

It is obvious from the summary in table 1 that the average change of each of the vascular elements studied in group 1 differed noticeably from the averages in groups 2 and 3. On the average, the changes in chronic left ventricular failure approximated the changes in mitral stenosis. The data are even more striking when the findings in mitral stenosis are compared with those of the two subdivisions of group 1 (table 2); it is apparent that the changes in calcific aortic stenosis associated with left ventricular failure were similar to those in mitral stenosis.

The most striking deviations from the control group occurred in the media of the muscular arteries in the other three groups. Averages for indexes of change in the intimal layer of these arteries were greatest in groups 1 and 4; however, the differences from control figures were not so great as in the case of the media of the muscular arteries. These findings conform to the observation of Larrabee and associates[2] that medial hypertrophy appears to be the earliest recognizable structural change in the small pulmonary vessels in mitral stenosis. It has been stated that the medial vascular changes in mitral stenosis are a true effect of the valvular disease, while accompanying intimal changes represent incidental aging processes. Our results would not appear to support unequivocally the latter opinion but suggest that one element responsible for the intimal change may be age.

It was noted that the indexes of change in 8 of the 24 cases of calcific aortic stenosis or systemic hypertension without left ventricular failure (group 2) were greater than those in certain cases in the group with chronic left ventricular failure (group 1). This may be explained in one of two ways. A simple explanation would be that left ventricular failure had been present in some cases in group 2 despite a negative history. The other possibility is that the vascular changes in the lungs may represent the anatomic expression of a functional response to left ventricular failure, a response which, although the left ventricle had failed, had prevented the occurrence of pulmonary edema and so had prevented the important clinical basis for the recognition or failure of the left ventricle.

It will be recognized that the argument just presented implies essentially the same explanation for the prevention of pulmonary edema in some cases of chronic left ventricular failure that has been applied for the prevention of pulmonary edema in mitral stenosis.[1] "Protective" contraction of the small pulmonary arterial vessels is considered to be the underlying factor responsible for the medial hypertrophy that was seen in the muscular arteries in cases of chronic left ventricular failure (group 1), in cases without ventricular failure (group 2) and in cases of mitral stenosis (group 4).

While it is recognized that great resistance to flow through small pulmonary arterial vessels in mitral stenosis is associated with medial hypertrophy of muscular arteries and is protective against the development of pulmonary edema, it is not known by what specific mechanism this arterial response is brought about. Similarly, while the mechanism for the hypertrophy of the muscular arteries seen in groups 1 and 2 is not understood, it is considered to be related to increased pulmonary venous pressure resulting from a failing left ventricle. The mechanism in these three groups is probably identical.

Summary

Structural vascular changes in the lungs in cases of chronic left ventricular failure were found to be qualitatively similar to those seen in mitral stenosis. The exact mechanism of the changes, the most striking of which was medial hypertrophy of the muscular arteries, is not known but would appear to be related to increase in left atrial and pulmonary venous pressures. Thus, the mechanism for the development of the pulmonary vascular changes in left ventricular failure appears to be like that operative in mitral stenosis.

Sumario Español

Los cambios estructurales en los pulmones en casos de descompensación crónica del ventrículo izquierdo fueron encontrados ser cualitativamente similares a aquellos observados en la estenosis mitral. El mecanismo exacto de estos cambios, el más significativo de los cuales fué la hipertrofia medial de las arterias musculares, no se sabe, pero aparece estar relacionado al aumento en la presión atrial izquierda y en la presión pulmonar venosa. De manera, que el mecanismo del desarrollo de cambios vasculares pulmonares en la descompensación ventricular izquierda aparenta operar similarmente a la estenosis mitral.

REFERENCES

[1] Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. **12:** 573, 1936.

[2] Larrabee, W. F., Parker, R. L., and Edwards, J. E.: Pathology of intrapulmonary arteries and arterioles in mitral stenosis. Proc. Staff. Meet., Mayo Clin. **24:** 316, 1949.

[3] Becker, D. L., Burchell, H. B., and Edwards, J. E.: Pathology of pulmonary vascular tree. II. Occurrence in mitral insufficiency of occlusive pulmonary vascular lesions. Circulation **3:** 230, 1951.

[4] Edwards, J. E.: Structural changes of the pulmonary vascular bed and their functional significance in congenital cardiac disease. Proc. Inst. Med. Chicago. **18:** 134, 1950.

[5] Israel, H. L.: Pulmonary hypertension and heart disease. Am. Practitioner & Digest. Treat. **1:** 367, 1950.

[6] Cournand, A.: Some aspects of the pulmonary circulation in normal man and in chronic cardiopulmonary disease. Circulation **2:** 641, 1950.

[7] Lagerlöf, H., and Werkö, L.: Studies on the circulation of blood in man. VI. The pulmonary capillary venous pressure pulse in man. Scandinav. J. Clin. & Lab. Invest. **1:** 147, 1949.

[8] Lewis, B. M., Houssay, H. E. J., Haynes, F. W., and Dexter, Lewis: The dynamics of both right and left ventricles at rest and during exercise in patients with heart failure. Circulation Research **1:** 312, 1953.

[9] Borden, C. W., Ebert, R. V., Wilson, R. H., and Wells, H. S.: Pulmonary hypertension in heart disease. New England J. Med. **242:** 529, 1950.

[10] Parker, R. L.: Pulmonary emphysema: A study of its relation to the heart and pulmonary arterial system. Ann. Int. Med. **14:** 795, 1940.

[11] White, P. D.: Weakness and failure of the left ventricle without failure of the right ventricle. J.A.M.A. **100:** 1993, 1933.

[12] Brenner, O.: Pathology of the vessels of the pulmonary circulation. Arch. Int. Med. **56:** 211; 457; 724; 976; 1189, 1935.

Treatment of Angina Pectoris with Cinchona Alkaloids

By JOSEPH E. F. RISEMAN, M.D., LESTER A. STEINBERG, M.D., AND GEORGE E. ALTMAN, M.D.

Reports indicating the value of quinidine sulfate in angina pectoris led to (1) a search for related drugs which were equally effective but less toxic, and (2) a study of the mode of action of these drugs. It was found that quinidine, quinine, cinchonadine, and cinchamidine decrease the frequency of attacks in daily life and increase the exercise tolerance as measured by a standardized test. Quinine sulfate (0.3 to 0.4 Gm. every eight hours) appears to be the drug of choice from the standpoint of availability and low toxicity as well as effectiveness. The value of these drugs is apparently due to a vasodilating action which in turn is dependent on the presence of the quinoline ring.

PREVIOUS studies[1–6] have demonstrated the value of quinidine sulfate in the treatment of some patients with angina pectoris. However, most general practitioners and, in fact, many cardiologists hesitate to use quinidine in angina because of the complications which occasionally follow its use in the treatment of cardiac arrhythmias. Furthermore, many physicians hesitate to use quinidine in angina pectoris because its mode of action in this condition is not clear. It seemed worthwhile, therefore, to study the activity of drugs related to quinidine in an attempt to find a substance equally effective but possibly less toxic and also to throw some light on the mechanism of action in the treatment of angina pectoris.

The comparative value of 12 pharmaceutical preparations was investigated in patients with angina pectoris. Five of these 12 were cinchona alkaloids (the sulfate salts of quinidine, quinine, cinchonine, cinchonidine, and cinchamidine); these were studied to determine whether drugs which were similar to quinidine in chemical structure but different in cardiodynamic and cardiotoxic effects were of therapeutic value in angina. Procaine amide (Pronestyl) was included because, like quinidine, it is of value in eliminating ectopic ventricular beats. Three synthetic antimalarial preparations (chloroquine, pentaquine and chlorguanide) were chosen to see whether the therapeutic action in angina might be related to the mechanism responsible for antimalarial activity. Nitroglycerin was used to determine which patients were likely to be benefited by vasodilator drugs and also to compare the effectiveness of the cinchona alkaloids with that of nitroglycerin which is the most effective of the drugs for angina. Pentaerythritol tetranitrate (Peritrate) was included to compare the frequency and degree of response of the cinchona alkaloids with that of a preparation currently advocated for the treatment of angina pectoris. Finally, placebos were used for control studies and to equalize the beneficial psychologic effects of treatment.

Evaluation of the efficacy of treatment in angina pectoris is difficult. Some of the many factors and problems involved in evaluating treatment in angina will be summarized elsewhere.[7] The methods employed in the present study are based on over 20 years' experience in the Angina Clinic of the Beth Israel Hospital of Boston. In general, these studies are carried out in a group of patients with angina carefully selected for cooperation and a stable clinical course. The methods include clinical evaluation (using what has been called the "double blind test") and, especially, an exercise tolerance test which measures the amount of work which can be done under standardized conditions (in the cold) before angina is in-

From the Medical Research Department of the Yamins Research Laboratory, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

This study was aided by a grant from the Cinchona Institute.

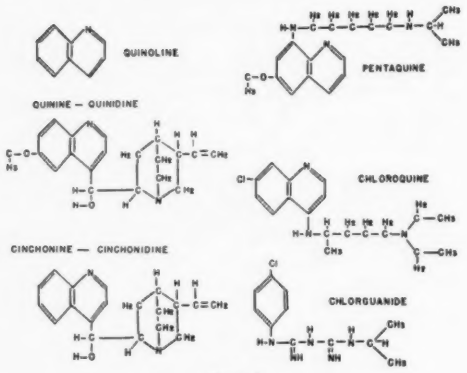


FIG. 1

duced. In addition, the work electrocardiogram after treatment was compared with that observed after placebos. Furthermore, the results with the drugs being evaluated were compared with those obtained with other medication in current use. In particular, the results were analyzed not only as observed in the entire group of subjects but also in subdivision based on the ability of the patients to respond to nitroglycerin.

MATERIALS AND METHODS

Medication

The Cinchona Alkaloids. Cinchona bark contains about 35 alkaloids of which five chemically related compounds are obtained in appreciable amounts during the process of extracting the commercially important quinine. *Quinine* and *quinidine* are optical isomers (fig. 1); the former is levorotatory (minus 169 degrees) the latter is dextrorotatory (plus 230 degrees). *Cinchonine* (plus 229 degrees) and *cinchonidine* (minus 109 degrees) are also optical isomers; these two drugs are similar to quinine and quinidine except for a methoxy group in the quinoline ring. *Cinchamidine* (minus 98 degrees) is similar to cinchonidine except for the presence of two hydrogen atoms in the side chain.

Quinidine is far more effective in the treatment of the cardiac arrhythmias than the other alkaloids found in cinchona bark[8, 9]; only four groups of investigators have reported on its use in angina pectoris.[1-6] The use of quinine (as "peruvian bark") in angina was reported[10] as early as 1795; while in 1842, Hope's textbook stated "Quina is the specific for intermittent angina."[11] The first experimental evaluation of the use of quinine in angina pectoris, however, did not appear until 1943.[3] So far as can be determined, the other cinchona alkaloids have not been used in angina pectoris.

The five cinchona alkaloids used in this study were prepared in Holland* in the form of 0.12 Gm. (2 grain) scored, compressed, white tablets, identical with each other in appearance. The dosage used in most instances was 0.360 Gm. (6 grains) or three tablets given three times daily; on arising, at 2.00 p.m., and on retiring. This interval was selected because it has been shown that eight hours after the administration of quinidine sulfate, the concentration in the blood[12] and the effect on the heart[13] are approximately one-half as great as the maximum. Thus, with 0.4 Gm. (6 grains) every eight hours the effective level in the blood is constantly as high as or higher than the maximum obtained with 0.12 Gm. (3 grains) given at four-hour intervals. Several patients who benefited from the 0.4 Gm. dosage were subsequently given smaller amounts in order to determine the minimum effective dose; patients who failed to respond to 0.4 Gm. were not given smaller doses. In order to check the results obtained with these tablets, quinidine sulfate, packaged by American Pharmaceutical houses in the form of 0.2 Gm. or 0.3 Gm. compressed tablets, and quinine sulfate in the familiar 0.3 Gm. chocolate coated tablets or 0.3 Gm. capsules were also used.

Nitroglycerin. The prophylactic value of nitroglycerin was determined two minutes after a 0.0003 Gm. (1/200 grain) hypodermic tablet had dissolved under the tongue. This, according to previous studies,[2] is the time when the maximum effect of sublingual nitroglycerin is evident.

Procaine amide hydrochloride was used in the form of yellow capsules containing 0.25 Gm. of Pronestyl.† The dosage employed was three capsules (0.75 Gm.) three times a day (at approximately eight-hour intervals).

Synthetic Antimalarial Preparations. Chloroquine‡ was obtained in the form of white compressed tablets of Aralen Diphosphate containing 0.25 Gm. each, and equivalent to 0.15 Gm. of chloroquine base. The dosage used was one tablet three times daily at approximately eight-hours intervals.

Pentaquine§ was used in the form of small, red, sugar coated tablets each containing 13.3 mg. of pentaquine phosphate equivalent to 10 mg. of pentaquine. The dosage was one tablet, three times daily, taken either alone or in some cases together with quinine sulfate, 0.12 Gm., (a dose of quinine usually too small to be of therapeutic effect in angina).

Chlorguanide was obtained as the hydrochloride‖

* These five alkaloids were furnished by the Cinchona Institute.

† Pronestyl was supplied by E. R. Squibb & Son.

‡ Aralen Diphosphate was supplied by Winthrop-Stearns Inc.

§ Pentaquine was supplied by The Abbott Laboratories.

‖ Chlorguanide was supplied by Sharpe and Dohme.

in the form of small white, compressed tablets of 0.1 Gm. each. These, also, were given three times daily.

Pentaerythritol tetranitrate was used in two forms; white tablets containing 10 or 20 mg. prepared for clinical investigation before the drug was placed on the market* and also green tablets containing 10 mg. of peritrate.† The drug was given in doses of 50 mg. four times daily (with meals and before retiring). Several Patients also received smaller doses.

Placebos of four varieties were used. Tablets of lactose, flavored with aloin (for bitterness) were prepared to resemble the cinchona alkaloids.‡ Sodium bicarbonate tablets simulated chlorguanide. Yellow capsules identical with Pronestyl and white tablets identical with pentaerythritol tetranitrate were supplied by the manufacturers. No attempt was made to duplicate, with placebos, the distinguishing markings on the Aralen, the red pentaquine or the green Peritrate tablets. The 15 forms in which the 12 types of medication were dispensed effectively prevented the patient from differentiating between noneffective and supposedly effective drugs through their physical appearance.

Subjects

The 32 subjects used in this study were selected from at least five times that number who were referred from the Medical and Cardiac Out-Patient Clinics of the Beth Israel Hospital, of Boston. The criteria for selection are discussed elsewhere.[7] All had angina pectoris, presumably due to arteriosclerosis of the coronary arteries; the distribution according to sex, age, symptoms and findings (table 1) shows them to be a typical group of such patients. Only four patients had neither hypertension, abnormal electrocardiograms, nor cardiac enlargement. All were ambulatory; 13, including 2 women, were gainfully employed in industry; of the remaining 19, the 8 women were able to do at least part of their housework; the 11 men were unemployed due to either their age or their illness.

Methods

All patients visited a special angina research clinic of the Beth Israel Hospital, regularly, at weekly intervals, except for occasional periods due to illness, vacations, or similar causes. The diagnosis, clinical history, frequency of attacks, precipitating factors, duration of periods of spontaneous freedom from attacks, and previous therapy were all re-evaluated both independently and collectively by three investigators. Twelve-lead electrocardiograms were repeated once a year and also whenever a change in clinical course suggested a change or progression of the underlying pathology.

TABLE 1.—*Distribution of Subjects*

	Age (years)					
	Total	30–39	40–59	50–59	60–69	70–79
Male	22	0	1	8	13	0
Female	10	1	0	6	2	1
	Duration of Angina Pectoris (years)					
	½–1	2–3	4–6	8–10	11–22	
Male	5	9	2	3	3	
Female	5	3	2	0	0	
	History of Previous Myocardial Infarction					
	None		Probable		Definite	
Male	8		4		10	
Female	6		1		3	
	Blood Pressure					
	110/76 to 140/88		145/90 to 165/98		175/100 to 210/130	
Male	9		4		9	
Female	5		0		5	
	Electrocardiogram at Rest					
	Normal		Right Bundle-Branch Block		Abnormal	
Male	10		2		10	
Female	7		1		2	
	Heart Size					
	Normal			Enlarged		
Male	13			9		
Female	1			9		

At each visit, the same observer interviewed each patient and ascertained: (1) the patient's evaluation of the effectiveness of the previously administered drug; (2) the actual number of attacks experienced during the previous week; (3), any changes in the patient's daily routine which might have influenced the frequency of attacks; (4) any untoward effects of medication. After the above interview, the exercise tolerance was measured under the standardized conditions used in previous studies[2-4, 7, 14-26] by one or both of the other observers, who, however, did not know what drug the patient was taking. All tests (except those following nitroglycerin) were carried out between one and two hours after the last medication, at least one hour after a light breakfast and following at least 20 minutes rest after coming to the clinic. All tests were carried out in a

* These experimental tablets were supplied by the Maltbie Laboratories, Inc.

† Peritrate was supplied by the Chilcott Laboratories.

‡ Supplied by Brewer & Company.

special cold room maintained at a temperature of 45 to 55 F. The exercise consisted of repeatedly ascending and descending a two-step staircase (each 9 inches high) until a typical attack of angina was induced or until the patient became fatigued or dyspneic or until the patient had done at least 50 per cent more work than was possible without medication. Only one test was performed on any one day. No test was performed if the patient had experienced an attack within one hour prior to the exercise (table 2).

After the first visit, each patient was given a placebo to be taken three times daily. Observation for several weeks to months established the usual frequency of attacks in daily life and, with some degree of accuracy, the standardized exercise tolerance following placebos. The evaluation of medication was then begun. Further checks of the patients' exercise tolerance while taking placebos was redetermined frequently during the course of the study.

At each visit, after the exercise tolerance had been measured, the patient returned to the original observer who supplied sufficient medication for the following week. In each instance it was stated or implied that the medication dispensed had been reported as effective in some cases with angina. No definite or constant order of rotation of the drugs was followed except that placebos were invariably given for several weeks before administering any potentially effective medication. If the studies failed to indicate any appreciable benefit, a different medication was prescribed. If the drug was followed by evidence of improvement (i.e., an increase in exercise tolerance of at least 20 per cent as compared with the maximum performed while taking placebos or when taking no medication), a placebo resembling the effective drug was again administered, often (especially with quinine and quinidine) with a different appearance.

Electrocardiographic Studies

After the therapeutic value of the drugs had been determined as above, electrocardiographic studies were carried out in some patients who showed a beneficial result in order to determine if the effect was accompanied by objective evidence of a decrease in myocardial anoxia.[18, 25]

In order to obtain tracings with a minimum of somatic tremor or wandering of the base line during and immediately after exercise, the arm electrodes were applied just below the insertion of the deltoids; the leg electrodes were applied over the bony prominence of the iliac crests; a precordial electrode (measuring 2½ by 1½ inches) was applied in the fifth left intercostal space at the midclavicular line, and the cable was held in the patient's right hand against his body. A direct recording Sanborn Electrocardiograph was used. Lead 4R only, was recorded.

Evidence of myocardial anoxia is most frequently and most strikingly shown by this lead because anoxia is associated with RS-T depression in V_4 and RS-T elevation in V_R while lead 4R is V_4 minus V_R. Only one lead was recorded on any one day because comparison of tracings before and after medication requires comparison of complexes observed at identical times after exercise.

A 15-second control tracing was taken with the patient standing at rest in the cold room. The exercise was then carried out in the usual manner, but with the electrodes and cable in place and the machine, but not the recording stylus, running constantly. The tracing was recorded immediately before the expected cessation of exercise and for 15 seconds thereafter; the end of exercise was marked. Additional 15 second strips were obtained, one, three, and five minutes after the cessation of exertion. In examining the tracings, the characteristics of 10 consecutive complexes without wandering of the base line were measured and the average obtained.

Before medication (while taking placebos), exercise was continued until a typical attack was induced After medication, exercise was stopped when the patient had performed the same number of trips as had induced angina while taking placebos.

Evaluation of Results

Three methods of evaluation were used and their results were correlated with each other. These three methods were: (1) The exercise tolerance; that is, the amount of work which could be performed (under the standardized conditions described above) before angina was precipitated. (2) The patient's evaluation of the efficacy of treatment. (3) the number of attacks experienced in daily life during each week of therapy. The results following medication were divided into four categories as follows:

Marked Response. This indicates that compared with the maximum amount of work which could be performed while taking placebos, the exercise tolerance in the laboratory was increased either by at least 50 per cent before the patient was forced to stop because of pain or by at least 25 per cent without inducing angina, the exercise being stopped because of dyspnea or fatigue. These results were accepted as indicating a marked response only if they could be obtained repeatedly. Such patients showed, clinically, either complete disappearance or a marked decrease in the frequency of attacks in daily life during the period of medication.

Moderate Response. The exercise tolerance in the laboratory was increased by 20 per cent to 49 per cent before the patient developed angina or the patient was able to do up to 25 per cent more work

TABLE 2.—*The Response to Medication in 32 Patients with Angina Pectoris. The Increase in the Amount of Work Which Could Be Performed under Standardized Conditions before an Attack Was Induced*

Subject	Sex	Miscellaneous Medication				Cinchona Alkaloids					Synthetic Antimalarials		
		Placebos S.E.T.T.* trips	Nitroglycerin	Pentaerythritol Tetranitrate	Procaine Amide	Quinidine	Quinine	Cinchonidine	Cinchamidine	Cinchonine	Chloroquine	Pentaquine	Chlorguanide
		Per Cent Increase in S.E. T.T.* Following Medication											
Group 1 Patients													
H St	M	12–16	210			112	100						
S R	M	36–40	170			42	×						
R S	M	17–20	120+			30	40						
M L	M	32–35	114			20	20						
H N	M	24–29	93+	28	3	38	31	3	45+R	10	52+R	38	0
R E	M	24–30	93	20	−3	13	17	7+	0+	0			
F B	F	12–16	88+		50	62	13	60	13	19	0	38	19
H Schl	M	34–40	87+			60+	×						
B K	F	18–20	60			25	60						
L W	M	36–40	53			35	3						
G H	M	25–33	52+	39	6	67+R	82+	61	67+	36			
M B	M	29–33	52+	−9	−12	27	12	36+	21	18	−6	6	−18
E R	F	20–27	48+	−11	−7	−11	103+R	4	41	4	55+	−30	
A T	F	18–27	48+	−15	−26	52	52	59	33	−33	67	26	0
A G	M	46–51	39+				0		−2	−29			
P S	M	23–28	32+	−43	7	25+R	43+R	29+	11	−25	43+	43+	0
Group 2 Patients													
R K	M	10–13	46	−15	−54	23	23		23	31			
E S	F	24–32	44	−19	−6	−19	−16	−19	−13	−6	−44	−13	
M La	M	10–14	43	−21		21	14	−21	14	7			
J S	M	19–24	42	−40	4	4	13	×	−25	×	0+R	−21	
S E	M	32–38	32			18+	8			5	5		
M E	M	24–26	23			15	8+						
T Mc	M	33–36	22	−17	−11	19	11	−6	8+	0	6	−17	−8
Group 3 Patients													
W T	M	23–30	17		−13	−17	−3	−10	0	23			
S W	F	24–27	11		−52	−11							
B A	M	38–40	3			33	5						
R B	F	8–10	0			−20	×						
K W	F	20–24	4	−50	4	25	0	29+	4	21	13	−4	29
M K	F	16–20	−10	−5	−20	10	5	−5	−15	−20	0	−15	−20
G W	M	18–24	−17			−17		−38	−21	−13			
J G	M	19–26	−35			−23	−8	−4		−4			
A L	F	7–11	−36	−45	−73	−36							

* Standardized exercise tolerance test.

\+ No attack was induced.

+R Following medication, attacks disappeared in daily life and could not be induced in the laboratory. This condition persisted for at least one month after medication was stopped.

− A decrease in standardized exercise tolerance.

× Medication discontinued because of untoward effect.

TABLE 3.—*The Degree of Response to Medication in 32 Patients with Angina Pectoris*

Medication	Total Patients Studied	Therapeutic Response of Patients							
		Marked Response		Moderate Response		Slight Response		No Response	
	No.	No.	%	No.	%	No.	%	No.	%
Miscellaneous									
Nitroglycerin	32	16	50	7	22	2	6	7	22
Pentaerythritol tetranitrate	15	0	0	3	20	0	0	12	80
Procaine Amide	17	1	6	0	0	0	0	16	94
Cinchona Alkaloids									
Quinidine	31	6	19	12	39	4	13	9	29
Quinine	26***	6	23	4	15	7	27	9	35
Cinchonidine	16*	6	38	1	6	0	0	9	56
Cinchamidine	18	2	11	7	39	2	11	7	39
Cinchonine	19*	0	0	4	21	2	11	13	67
Synthetic Antimalarials									
Chloraquine	12	4	33	1	9	1	9	6	50
Pentaquine	11	1	9	3	27	0	0	7	54
Chlorguanide	8	0	0	1	13	1	13	6	75

* One patient and *** three patients respectively discontinued medication because of untoward effects. This result is considered as No Response.

than was possible while taking placebos, the exercise being stopped not by pain but by dyspnea or fatigue. These results were accepted only if they could be repeated. Such patients usually reported a decrease in the frequency of attacks in daily life.

Slight Response. These patients were able to do from 10 per cent to 19 per cent more work in the laboratory before developing angina. This degree of response was of no demonstrable clinical significance.

No Response. This indicates less than a 10 per cent increase in exercise tolerance.

RESULTS

In accordance with our previous experience[2] the results of the standardized exercise tolerance test proved to be the most valuable method of measuring the response to therapy. There was a close correlation between an increase in the standardized exercise tolerance test in the laboratory and the response in daily life, in that marked or moderate improvement in exercise tolerance was always associated with a decrease or disappearance of attacks in daily life. On the other hand, most patients felt that they were helped by treatment irrespective of the medication used, and a decrease or disappearance of attacks in daily life was not always accompanied by an increase in exercise tolerance. Thus apparent clinical improvement occurred much more frequently than did objective evidence of real improvement. This is in accord with other studies in the literature[27, 28] which indicate that patients are unable to differentiate between the response to active therapy and the response to placebos. According to the patients' evaluation of the efficacy of treatment, 23 (of the 32) believed that they were helped by each of the many drugs prescribed, including placebos. There were five patients who believed that some, but not all, medication was helpful; the weeks of poor response, however, were often related to noncardiac symptoms or emotional experiences and could not be correlated with either the medication or the actual number of attacks experienced. The remaining four patients believed that they were not helped by any medication; two of these four actually failed to respond to any therapy.

Similarly, there was no constant correlation between the actual number of attacks experienced during a given week of treatment and either the patient's estimation of the response to treatment or the exercise tolerance. The clinical course of angina is rarely uniform, and patients who have several attacks weekly frequently experience a week or two of complete freedom from attacks irrespective of treatment. At the onset of the study, when a written record of the frequency of attacks was instituted, most patients reported fewer episodes per week than had been estimated previously. Since this decrease came while taking placebos, the apparent improvement was due not to specific therapy but rather to psychologic factors and more careful observation. Subsequently patients frequently reported further improvement without, however, any change in the actual frequency of attacks.

In general, clinical improvement occurred frequently without objective evidence of improvement and repetition of the same therapy frequently gave different clinical results. An increase in exercise tolerance of more than 20 per cent, however, was practically always accompanied by clinical improvement and such results could be duplicated when the therapy

was repeated even if the appearance of the medication was different.

The usual number of trips which could be performed under standardized conditions by each patient while taking placebos and the change following medication are shown in table 2. The change in ability to work following medication is expressed as the percentage increase (or decrease) in exercise tolerance as compared with the maximum number of trips which could be performed while taking placebos. The frequency with which medication was followed by a decrease in exercise tolerance indicated that this base line is on the high side of his usual exercise tolerance and does not indicate that the patient was made worse by the medication.

Miscellaneous Control Studies

Placebos. Each of the 32 patients received many courses of at least three different placebos during the investigation. The usual range of exercise tolerance was relatively constant. A variation of 2 to 4 trips was observed in 18 patients, from 5 to 6 trips in eight patients and from 7 to 9 trips in the remaining six patients. Thus, the variation from the average standardized exercise tolerance was plus or minus 2 to 9 per cent in 15 patients, plus or minus 11 to 14 per cent in 13 patients and plus or minus 16 to 22 per cent in the remaining four patients.

Nitroglycerin. Between 20 and 30 seconds were required for the 0.0003 Gm. hypodermic tablets of nitroglycerin used in this study to dissolve under the patients' tongue. When the standardized exercise tolerance was measured two minutes later, 23 of the 32 were able to do an appreciably greater amount of work than was possible when they were taking placebos alone. The prophylactic use of nitroglycerin made it possible to divide patients into three groups as described previously[4, 26]: Group 1 (16 patients or 50 per cent) included those who, following the sublingual administration of nitroglycerin, were able to exercise either to the point of fatigue without experiencing angina or who could do at least 50 per cent more work (under the standardized conditions of the test) than was possible without nitroglycerin. Group 2 (seven patients or 22 per cent) included those who were able to do 20 per cent to 49 per cent more work than was possible without this drug but who, nevertheless, developed a typical attack of angina pectoris. Group 3 (nine patients or 28 per cent) could do no more work (or less than 20 per cent more work) after the sublingual administration of nitroglycerin than was possible without the drug. The patients' response to nitroglycerin was an index of the likelihood of his response to other effective medication; the results, therefore, are examined accordingly (tables 3 and 5).

Pentaerythritol Tetranitrate. Fourteen patients received 50 mg. of this preparation, four times daily; only three showed objective evidence of a favorable response. All three patients were group 1 subjects; the degree of response was moderate in degree (an increase in exercise tolerance of 20, 28, and 39 per cent, respectively).

Procaine Amide Hydrochloride. Seventeen patients received 750 mg. of this drug, three times daily. Only one showed a beneficial response. Subsequent observation in this patient suggests that this apparent response was due, not to the medication, but rather to a spontaneous partial remission, for her exercise tolerance, even after several months of placebos, had not returned to its original range.

Two of the 17 patients who received procaine amide showed ventricular extrasystoles during their attacks of angina pectoris. The lack of improvement of the angina in these two patients following procaine amide is in contrast to the favorable response reported by Davis in one patient.[6]

The Cinchona Alkaloids

Quinidine, quinine, cinchonidine, and cinchamidine were of considerable value in angina pectoris while cinchonine was of only slight value. In several patients an attempt was made to determine the minimum effective dose. Doses of 0.12 Gm. given at the same time intervals proved of little value. Doses of 0.25 Gm. were usually (but not always) as effective as was 0.3 Gm. or 0.4 Gm.

Quinidine sulfate was administered to 31

TABLE 4.—*The Efficacy of Medication in 23 Patients Who Were Likely to Respond and Also in Nine Patients Who Were Not Likely to Respond*

Medication	Total Patients Studied	Groups 1 and 2			Group 3		
		No. of Pts.	Marked or Moderate Response %	Slight or No Response %	No. of Pts.	Marked or Moderate Response %	Slight or No Response %
Miscellaneous							
Nitroglycerin	32	23	100	0	9	0	100
Pentaerythritol Tetranitrate	15	12	25	75	3	0	100
Procaine Amide	17	12	8	92	5	0	100
Cinchona Alkaloids							
Quinidine	31	22	73	27	9	22	78
Quinine	26***	21**	47	53	5*	0	100
Cinchonidine	16*	11*	55	45	5	20	80
Cinchamidine	18	14	64	36	4	0	100
Cinchonine	19*	14*	14	86	5	40	60
Synthetic Antimalarials							
Chloroquine	12	10	50	50	2	0	100
Pentaquine	11	9	44	56	2	0	100
Chlorguanide	8	6	0	100	2	50	50

* One additional patient discontinued medication because of untoward effects.
** Two additional patients discontinued medication because of untoward effects.
*** Three additional patients discontinued medication because of untoward effects.

patients. A significant increase in exercise tolerance was shown by 18 of the 31 (58 per cent); these patients included 16 of the 22 subjects in groups 1 and 2 (73 per cent).

In many instances, the increase in exercise tolerance induced by quinidine persisted for two to three weeks after the drug was withdrawn. This is in contrast with our experience with other drugs such as the purines[2, 30] where any improvement usually disappears within one week. Two patients had a *complete* remission of symptoms: that is, following quinidine therapy they experienced no attacks in daily life, and they were able to exercise until fatigued without developing angina under the usual standardized conditions. In these patients, this remission persisted for at least two months after placebos were substituted for quinidine. In both instances, readministration of quinidine at a later date was again followed by a complete but temporary remission.

Quinine sulfate was given to 29 patients, 3 of whom discontinued the medication. Of the remaining 26, a moderate or marked response was shown by 10 (38 per cent); these 10 were all patients of groups 1 and 2 and constituted 47 per cent of the 21 patients in these two groups. Two patients experienced a temporary remission of angina following quinine.

The comparative value of quinine and quinidine is best shown by the 25 patients whose response to both drugs was tested (table 5). Of these 25 patients, the results in 15 (60 per cent) were identical; four additional patients (16 per cent) showed a response to both drugs but a better response to one than to the other. The remaining six patients (24 per cent), showed a moderate or marked response to one drug but no appreciable response to the other.

Cinchonidine sulfate was administered to 17 patients, one of whom omitted the drug. Of the remaining 16 patients, 7 (44 per cent) showed a moderate or marked response; six of these patients were in group 1 (these six made up 55 per cent of the group 1 and 2 patients who received cinchonidine).

Cinchamidine sulfate was given to 18 patients; nine (50 per cent) had a moderate or marked response. All of these nine were in groups 1 and 2 (64 per cent).

Cinchonine sulfate was given to 20 patients, one of whom discontinued its use. Only four of these patients showed a moderate response; no patient showed a marked response.

TABLE 5.—*Comparison of Results in 25 Patients Who Received Both Quinidine Sulfate and Quinine Sulfate*

Group 1 Patients			Group 2 Patients			Group 3 Patients		
Subject	Increase in S.E.T.T. %		Subject	Increase in S.E.T.T. %		Subject	Increase in S.E.T.T. %	
	Quinidine	Quinine		Quinidine	Quinine		Quinidine	Quinine
H St	112	100	R K	23	23	W T	−17	−3
R S	30	40	E S	−19	−16	B A	33	5
M L	20	20	M La	21	14	K W	25	0
H N	38	31	J S	4	13	M K	10	5
R E	13	17	S E	18+	8	J G	−23	−8
F B	62	13	M E	15	8+			
B K	25	60	T Mc	19	11			
L W	25	3						
G H	67+ R	82+						
M B	27	12						
E R	−11	103+ R						
A G	52	52						
P S	25+ R	43+ R						

S.E.T.T. Standardized exercise tolerance test.
− A decrease in exercise tolerance.
+ No attack induced.
+ R Clinical remission of symptoms.

Untoward reactions were not common and not severe. They usually disappeared with a decrease in dosage. Three patients discontinued the use of quinine, and one patient discontinued both cinchonidine and cinchamidine because of tinnitus or dizziness. This is discussed further, below.

Synthetic Antimalarial Preparations

Chloroquine was given to 12 patients, 5 (42 per cent) of whom responded to a moderate or marked degree; all five were in groups 1 or 2 (50 per cent).

Pentaquine phosphate was given to 11 patients, 4 (36 per cent) of whom responded; all four were in groups 1 and 2 (44 per cent). Because the combination of quinine and pentaquine has been reported to be especially beneficial in the treatment of malaria,[29] six patients were given a combination of quinine, 0.12 Gm., plus pentaquine, 13.3 mg., three times daily; the combination showed no synergistic effect. Because of the toxicity of pentaquine, further studies were discontinued.

Chlorguanide hydrochloride was given to eight patients. Only one showed a moderate increase in exercise tolerance. This probably does not represent a true response in this patient but rather a spontaneous partial remission, for the patient continued to have an increased exercise tolerance for six months, and readministration of chlorguanide caused no further increase in ability to exercise.

TABLE 6.—*The Effect of Medication of the Electrocardiographic Changes Induced by Exercise*

Subject	No. of Trips	mm. depression of RS-T segments (average of 10 consec. complexes)				
		Placebos	Nitroglycerin	Quinidine	Quinine	Cinchamidine
T. Mc.	32	3.5*	1.25	1.25		
E. R.	29	3.0*	1.5		2.25	2.0
P. S.	28	2.0*	0.0		0.75	
A. T.	26	1.5*	0.25	1.0	0.75	1.5
M. B.	32	0.5*	0.25			0.0

* Attacks of angina were induced by this amount of work only when these patients were taking placebos.

Electrocardiographic Studies

Electrocardiographic studies were carried out in five patients in groups 1 and 2 while they were taking placebos, nitroglycerin, quinidine, quinine or cinchamidine (table 6, fig. 2). The most striking change in lead 4R was observed immediately (within 15 seconds) after the cessation of exercise and consisted of a depression of the RS-T segments; this is in accord with previous studies.[25]

In these five patients, nitroglycerin not only

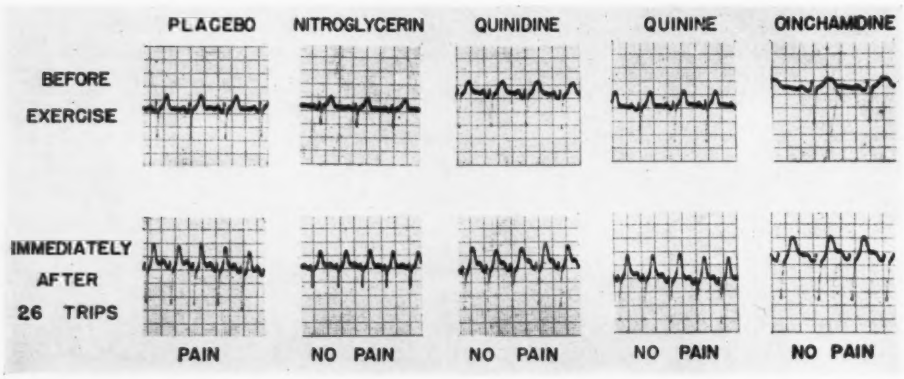


FIG. 2. Electrocardiographic studies in patient A. T.

prevented attacks of angina, but also decreased markedly the RS-T depression. The average RS-T depression following exercise was 2.1 mm. while taking placebos and 0.65 mm. after nitroglycerin. In general, those who showed the greatest RS-T changes while taking placebos showed the greatest improvement in the exercise electrocardiogram after nitroglycerin.

The RS-T depressions of the two patients who benefited from quinidine were 3.5 mm. and 1.5 mm., respectively, while taking placebos, as compared with 1.25 mm. and 1.0 mm., respectively, while taking quinidine. Similarly, the three patients who benefited from quinine showed RS-T depressions of 3.0 mm. 2.0 mm. and 1.5 mm. before, and 2.25 mm. 0.75 mm. and 0.75 mm., respectively, after this drug. The results with cinchamidine, although not so striking, also showed a diminution of the anoxic changes in the exercise electrocardiogram; the RS-T depressions measured 3.0 mm. 1.5 mm. and 0.5 mm. following placebos and 2.0 mm. 1.5 mm. and 0.0 mm., respectively, following cinchamidine.

COMMENT

Evaluation and Significance of Results

The above studies illustrate the importance of adequate control studies in measuring the value of treatment in angina pectoris, and also the advisability of comparing the effect of the drug under study with the effects of other medication of accepted or potential value. By this means we can clearly demonstrate the contrast between the negative results obtained with three of the preparations (placebos, procaine amide, and chlorguanide), the moderately favorable results with two drugs (cinchonine and pentaerythritol tetranitrate) and the positive results obtained with seven other drugs (nitroglycerin, quinidine, quinine, cinchonidine, cinchamidine, chloroquine and pentaquine); this contrast emphasizes the significance of the results with the latter seven drugs.

These studies also illustrate the value of considering separately the results obtained in patients likely to respond to medication and in those not likely to react favorably. Thus, of the 16 patients who showed a marked response to nitroglycerin, nine showed a marked response and six more showed a moderate response to one or more of the cinchona alkaloids. Similarly, of the seven patients who showed a moderate response to nitroglycerin, six showed a moderate response to other drugs. In contrast, only two of the nine patients who showed no response to nitroglycerin showed a moderate response to other drugs. In our experience, the frequency of group 3 patients has varied from 28 per cent of the subjects in the present study to 40 per cent in previous studies with larger numbers of subjects.[26] Unless the negative results in these nonreacting patients are separated from the results obtained in patients more likely to respond to medication, the beneficial results in the latter group are likely to be overlooked or minimized because of dilution with negative results.

It is advisable to compare the efficacy of the cinchona alkaloids with that of other therapy used in angina. From the results of the above and also from the results of previous studies, nitroglycerin ranks highest in the frequency and the magnitude of its prophylactic effect in angina pectoris; its practical value is limited, however, by its relatively short duration of action.[2] Pentaerythritol tetranitrate is obviously of some value in some patients, but it is much less effective than other available drugs including some of the cinchona alkaloids. Comparison with previous studies indicates that the effectiveness of the cinchona alkaloids is of the same magnitude as that of nonenteric coated theobromine sodium acetate and aminophylline in appropriate doses[15] and is considerably greater than that of oral papaverine[21] or khellin.[30] The cinchona alkaloids rank, therefore, among the most effective of medicinal agents available for the treatment of angina pectoris.

Mechanism of Action

The pharmacologic action of the cinchona alkaloids is incompletely understood even in the treatment of malaria in which it has been used for centuries. They have been called "general protoplasmic poisons," presumably because of their varied action on so many different tissues and organisms and especially because of their antiseptic action on many unicellular organisms (bacteria, yeast, infusoria, plasmodia, trypanosomes, spirochetes, amebae and spermatozoa). The use of this term "protoplasmic poison" is unfortunate, for it contributes to the fear of employing these drugs and it minimizes the fact that, like other drugs which may be toxic under some circumstances, they are valuable therapeutic agents when used properly.

It is probable that the cinchona alkaloids are effective in angina pectoris because of a vasodilator action. Thus, they are more effective in patients who respond to nitroglycerin and are least effective in patients who fail to respond to nitroglycerin. Furthermore, when these drugs are effective they also prevent or decrease the electrocardiographic evidence of anoxia induced by exercise. That quinidine and quinine have a vasodilating action is indicated by coronary blood flow studies in laboratory animals.[31]

It is probable that the cinchona alkaloids owe their effectiveness in angina pectoris to the presence of the quinoline ring (fig. 1). This would explain why chloroquine and pentaquine are also effective while chlorguanide, which has a phenol rather than a quinoline ring, is of no value. In this regard, it is of interest to note that papaverine, ethaverine, and pavril also contain the quinoline ring and are also of value in angina pectoris although the latter three are much less effective in angina pectoris than are the cinchona alkaloids.[21, 30]

The quinoline nucleus, together with many of its derivatives, possesses varied pharmacologic activity inducing antiseptic, anesthetic, and circulatory effects and a depressant action on the nerve endings.[31–34] Advantage is taken of these properties in therapeutics. The antiseptic properties are employed in preservatives (e.g., chinosol), amebicides (e.g., Vioform) and antimalarials (e.g., quinine). The anesthetic effects are seen with some quinine salts and especially Nupercaine. The circulatory effects have been incompletely studied, but include slowing of the heart, increase in the refractory period and vasodilation which is antagonistic to the action of epinephrine.[33, 34] The effect on the nerve endings has been suggested as the mode of action of quinine and quinidine in night cramps.[35, 36] The many quinoline derivatives each possess all of these activities in varying degrees although one effect may outbalance the others so as to seem quite specific. Thus quinidine is much more effective in the treatment of arrhythmias than the other cinchona alkaloids, and cinchonine is less effective in angina pectoris. Quinoline itself (as 8-hydroxyquinoline sulfate) has been found to be of slight value in angina pectoris.[30]

The possible roles of other mechanisms in achieving therapeutic results in angina pectoris deserve comment. Quinidine and also procaine amide have been advocated for the treatment of angina pectoris where exertion induces ventricular premature beats.[1, 5, 6] It is unlikely that the beneficial results observed in the present series are due to this action, for few

of the patients developed premature beats on exertion or during attacks, and procaine amide was not found of value in the present group. Furthermore, it has been shown that in the treatment of arrythmias (auricular fibrillation, for example), quinidine is far more effective than are quinine, cinchonidine, or cinchamidine,[8, 9] whereas in angina pectoris these drugs are almost equal in value.

The similarity of the clinical effectiveness of quinine and quinidine in both angina pectoris and in night cramps (which are not infrequent in patients with angina) is of interest. It is presumed that in night cramps the cinchona alkaloids act by blocking the nerve impulses at the myoneural junction.[35, 36] The evidence that this is the sole mode of action is far from conclusive, however, and the possibility of other pharmacologic activity which may be of value in both conditions, deserves further study.

Toxic and Untoward Effects

The potential toxicity, as well as the usual safety of the cinchona alkaloids is well known owing to their widespread use in the treatment of malaria. For convenience, the undesired reactions may be divided into A, the toxic or more serious effects, and B, the untoward or less serious effects.

A. *Toxic Effects.* These include the reactions which are potentially dangerous to life and necessitate immediate cessation of cinchona therapy. In our experience, with this series and with a large number of patients treated with quinidine since 1937, such reactions are rare in patients with angina pectoris. They include:

1. *Hypersensitivity Reactions.* Shortly after an initial dose of one of these cinchona alkaloids a patient may show collapse, asthmatic breathing, and other signs due to an inherent or acquired hypersensitivity. Such reactions are, fortunately, very rare; they occur with many other drugs as well. We have not, as yet, observed such reactions in patients with angina pectoris.

2. *Toxic Cardiac Effects.* The frequency of complications and deaths arising from the use of quinidine in the treatment of cardiac arrhythmias, especially chronic auricular fibrillation,[3] is well known and is probably the main reason why many physicians hesitate to use this drug. We have never encountered this type of reaction with the use of quinidine in the treatment of large numbers of patients with angina pectoris and normal cardiac rhythm. Auricular fibrillation is relatively uncommon in patients with angina pectoris; quinidine should not be used in such patients. These and other cardiotoxic effects of quinidine will probably be extremely rare with the other cinchona alkaloids including quinine.

3. *Miscellaneous Toxic Reactions.* After one or more days of therapy, a patient may develop thrombocytopenic purpura or fever or other symptoms indicative of a toxic effect on the hemopoietic or other systems. Here again, this type of reaction is rare. In over 16 years of using quinidine for the treatment of angina pectoris we have encountered one instance of fever in the treatment of a patient not included in the present series. Approximately 10 days after taking 0.6 Gm. of quinidine sulfate three times daily, this 56 year old woman with angina pectoris and ventricular extrasystoles developed malaise, a temperature of 103 F. and a generalized morbilliform rash. This all subsided within 48 hours after the drug was discontinued. In addition to this case there are a total of 14 others reported in the literature.[37]

B. *Untoward Effects.* These include the reactions which are uncomfortable but rarely dangerous to life. They usually disappear with a decrease in dosage, and they do not necessitate omission of therapy.

1. *Diarrhea* is the most common untoward reaction to these drugs; it is rarely troublesome and disappears quickly with a decrease in dosage to 2 or 3 grains three times daily. Many patients welcome this looseness of the bowel movements as a change from a habitually more constipated state; in fact, several patients have asked, "Please give me that good physic that you gave me last week." It is probably best to avoid its occurrence, for it may prevent adequate absorption of the drug.

2. *Nausea* may be very troublesome in an occasional patient. It usually disappears, however, with a decrease in dosage. Antacids may help.

3. *Tinnitus* is mentioned in all textbooks of pharmacology. It is not common in our experience even when patients received 1.1 Gm. daily for weeks or months. Two patients in the present series, however, discontinued quinine because of ringing in the ears.

4. *Dizziness* was complained of by one patient who had adverse comments to make about all therapy including placebos. Because of dizziness he discontinued the use of both cinchonidine and cinchamidine.

5. *Urticaria* was the most troublesome of the untoward effects, but here again it may disappear with a decrease in dosage. It caused two patients to discontinue quinine. It did not appear until the drug had been administered for the second time; this suggests that the reaction may be due to an acquired sensitivity.

Summary and Conclusions

1. The efficacy of 12 preparations in the treatment of angina pectoris was studied in 32 subjects with such symptoms.

The preparations included placebos, nitroglycerin, five cinchona alkaloids (quinidine, quinine, cinchonidine, cinchonine, and cinchamidine), procaine amide, chloroquine, pentaquine, chlorguanide, and pentaerythritol tetranitrate.

The methods of evaluation included: (a) a comparison of the clinical response with measurements of the exercise tolerance under standard cold conditions, and studies of the effect of medication on the electrocardiographic changes induced by exercise; (b) comparison of the value of the cinchona alkaloids with the ineffective placebos, the very effective nitroglycerin and the slightly effective pentaerythritol tetranitrate, and (c) analysis of the results in two separate groups of subjects, that is, those likely to respond to vasodilator therapy and those not likely to respond to such therapy.

2. Four of the cinchona alkaloids (quinidine, quinine, cinchonidine, and cinchamidine) proved to be highly effective in some but not all patients with angina. The patients most likely to respond to these cinchona alkaloids were those who responded well to nitroglycerin. No toxic and few untoward effects were observed.

Quinidine and quinine are among the most effective of the drugs now available for the treatment of angina pectoris.

3. Quinine is the drug of choice because of low toxicity, effectiveness, and low cost to the patient. Quinine possesses little of the potential cardiotoxic effects of quinidine. The latter drug is equally available but somewhat higher in cost. Quinidine is possibly somewhat more effective in angina than is quinine.

4. The effectiveness of the cinchona alkaloids in angina pectoris is due, at least in part, to a vasodilator action. The quinoline ring is probably the portion of the molecule primarily responsible for the therapeutic effect.

Sumario Español

1. La eficacia de 12 preparados en tratamiento de angina de pecho fué estudiada en 32 sujetos con tales síntomas.

Los preparados incluyeron placebos, nitroglicerina, cinco alkaloides de cinchona (quinidina, quinina, cinchonidina, cinchonina y cinchamidina), amida de procaína, cloroquina, pentaquina, cloroguanida y el pentaeritrol tetranitrito.

Los métodos de evaluación incluyeron: (a) una comparación en la repuesta clínica con medidas de tolerancia al ejercicio bajo condiciones uniformes de frío y estudios de efecto de el preparado en los cambios electrocardiográficos inducidos por el ejercicio; (b) comparación del valor de los alkaloides de cinchona con los placebos inefectivos, la muy efectiva nitroglicerina y el muy ligeramente efectivo pentaeritrol tetranitrito y (c) análisis de los resultados en dos grupos separados de sujetos, esto es, aquellos que probablemente responderían a la terapia vasodilatadora y aquellos que probablemente no responderían a tal terapia.

2. Cuatro de los alkaloides de cinchona (quinidina, quinina, cinchonidina y cinchamidina) probaron ser altamente efectivos en algunos pero no en todos los pacientes con angina. Los pacientes que con mayor probabilidad respondían a los alkaloides de cinchona fueron aquellos que respondieron bien a la nitroglicerina. Ningún efecto tóxico y pocos no deseables fueron observados.

La quinidina y la quinina estan entre las drogas más efectivas disponibles para el tratamiento de la angina de pecho.

3. La quinina es la droga preferida por su baja toxicidad, efectividad y bajo costo para el paciente. La quinina posee poco de los efectos potenciales cardiotóxicos de la quinidina. La última droga es igualmente disponible pero algo más alta en costo. La quinidina es posiblemente algo mas efectiva en la angina que la quinina.

4. La efectividad de los alkaloides de cinchona en la angina de pecho se debe, por lo menos en parte, a acción vasodilatadora. El anillo de quinolina es probablemente la porción de la molécula primariamente responsable por su efecto terapeútico.

REFERENCES

[1] Proger, S. H., Minnich, W. R., and Magendants, H.: The circulatory response to exercise in patients with angina pectoris. Am. Heart J. **10:** 511, 1935.

[2] Riseman, J. E. F., and Brown, M. G.: Medicinal treatment of angina pectoris. Arch. Int. Med. **60:** 100, 1937.

[3] —: The treatment of angina pectoris. A summary of ten years' objective study. New England J. Med. **229:** 670, 1943.

[4] Freedberg, A. S., Riseman, J. E. F., Spiegl, E. D.: Objective evidence of efficacy of medicinal therapy in angina pectoris. Am. Heart J. **22:** 494, 1941.

[5] Porter, W. B.: Probably grave significance of premature beats occurring in angina pectoris. Am. J. M. Sc. **216:** 509, 1948.

[6] Davis, D.: Angina pectoris associated with ventricular bigeminy, controlled by procaine amide. New England J. Med. **247:** 673, 1952.

[7] In preparation.

[8] Frey, W.: Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin. Berlin klin. Wchnschr. **55:** 450, 1918.

[9] Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C.: Observations upon the action of certain drugs upon fibrillation of the auricles. Heart **9:** 207, 1922.

[10] Black, S.: Case of angina pectoris, with remarks. Mem. Med. Soc. London **4:** 261, 1795.

[11] Hope, J.: A Treatise on the Diseases of the Heart and Great Vessels and on the Affections which may be Mistaken for Them. (First American from the Third London Edition.) Philadelphia, Haswell & Johnson, 1842.

[12] Linenthal, A. J., and Freedberg, A. S.: Measures used in the prevention and treatment of cardiac arrhythmias. New England J. Med. **241:** 612, 1949.

[13] Sagall, E. L., Horn, C. D., and Riseman, J. E. F.: Studies on the action of quinidine in man. I. Measurement of the speed and duration of the effect following oral and intramuscular administration. Arch. Int. Med. **71:** 460, 1943.

[14] Riseman, J. E. F., and Stern, B.: Standardized exercise tolerance test for patients with angina pectoris on exertion. Am. J. M. Sc. **188:** 646, 1934.

[15] Brown, M. G., and Riseman, J. E. F.: Comparative value of purine derivatives in treatment of angina pectoris. J.A.M.A. **109:** 256, 1937.

[16] Riseman, J. E. F., and Brown, M. G.: Duration of attacks of angina pectoris on exertion and effect of nitroglycerin and amyl nitrite. New England J. Med. **217:** 470, 1937.

[17] —, and —: Effect of oxygen on exercise tolerance of patients with angina pectoris. Am. Heart J. **18:** 150, 1939.

[18] Freedberg, A. S., Spiegl, E. D., and Riseman, J. E. F.: Octyl nitrite in the treatment of angina pectoris. Am. Heart J. **22:** 519, 1941.

[19] —, —, and —: Effect of external heat and cold on patients with angina pectoris: evidence for existence of reflex factor. Am. Heart J. **27:** 611, 1944.

[20] Freedberg, A. S., and Riseman, J. E. F.: Cobra venom in the treatment of angina pectoris. New England J. Med. **233:** 462, 1945.

[21] Gray, W., Riseman, J. E. F., and Stearns, S.: Papaverine in the treatment of coronary artery disease. New England J. Med. **232:** 389, 1945.

[22] Stearns, S., Riseman, J. E. F., and Gray, W.: Alcohol in the treatment of angina pectoris. New England J. Med. **234:** 578, 1946.

[23] Sagall, E. L., Kurland, G. C., and Riseman, J. E. F.: The effect of age on the clinical effectiveness of nitroglycerin tablets. New England J. Med. **235:** 650, 1946.

[24] Freedberg, A. S., and Riseman, J. E. F.: Observations of the carotid sinus reflex and angina pectoris. Circulation **7:** 58, 1953.

[25] Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The electrocardiogram during attacks of angina pectoris: its characteristics and diagnostic significance. Am. Heart J. **19:** 683, 1940.

[26] —: The present status of treatment in angina pectoris. Connecticut M. J. **9:** 99, 1945.

[27] Gold, H., Kwit, N. T., and Otto, H.: The xanthines (theobromine and aminophylline) in the treatment of cardiac pain. J.A.M.A. **108:** 2173, 1937.

[28] Silber, E. M., and Katz, L. N.: Coronary dilators and angina; reappraisal. J.A.M.A. **153:** 1075, 1953.

[29] COGGESHALL, L. T., AND RICE, F. A.: Cure of chronic vivax malaria with pentaquine. J.A.M.A. **139:** 437, 1949.

[30] Unpublished data.

[31] HEDBOM, K.: Ueber die Einwirkung verschiedener Stoffe suf das isolirte Saugethierherz. Skandinav. Arch. f. Physiol. **8:** 169, 1898.

[32] STARR, I., JR.: A note on the antagonism between the cardiac action of acetyl-B-methylcholine and acetyl choline and that of quinidine. J. Pharmacol. & Exper. Therap. **56:** 77, 1936.

[33] VON OETTINGEN, W. F.: The Therapeutic Agents of the Quinoline Group. Am. Chem. Soc. Monograph Series #64. New York, Chemical Catalogue Co., 1933.

[34] GOODMAN, L., AND GILMAN, A.: The Pharmacological Basis of Therapeutics. New York, MacMillan, 1941.

[35] Moss, H. K., AND HERRMANN, L. G.: Use of quinine for relief of "night cramps" in the extremities. J.A.M.A. **115:** 1358, 1940.

[36] —, AND —: Night cramps in human extremities. Am. Heart J. **35:** 403, 1948.

[37] SPRAGUE, H. W., AND TANSAY, W. A.: Fever as a sign of quinidine toxicity. New England J. Med. **249:** 795, 1953.

Traumatic Aortic Aneurysms

By Edwin M. Goyette, Col., MC, Hu A. Blake, Maj., MC, James H. Forsee, Col., MC, and Henry Swan, M.D.

Aneurysm of the thoracic aorta may follow severe, nonpenetrating injuries of the thorax unaccompanied by rib fractures. The aneurysms characteristically appear in the first portion of the descending aorta or less commonly in the proximal ascending portion. A large aneurysm, progressive enlargement, or symptoms may necessitate excision or repair. Such repair is now feasible. Traumatic aortic aneurysm should be considered in the differential diagnosis of obscure lesions in the thorax when there is a history of severe antecedent trauma.

TRAUMATIC AORTIC ANEURYSMS may be produced by blunt trauma or by penetrating wounds. Only those produced by nonpenetrating injuries will be discussed.

Traumatic rupture of the thoracic aorta was formerly thought to be rare and to result generally in sudden death, the diagnosis being possible only at autopsy.[1] With the development of angiocardiography and the popularization of exploratory thoracotomy, it is now possible to diagnose such injuries in the living patient. A few reports of such diagnoses have appeared in the recent literature and one survival for seven years has been reported.[2–4] Recent advances in aortic surgery have demonstrated the feasibility of repairing traumatic aneurysms of the aorta and successful resections have been reported by Bahnson[5] and by Johnston and associates.[6]

Aneurysms of the thoracic aorta may be produced by compression injuries of the thorax and by blows with blunt objects which do not produce rib fracture or obvious bruising of the chest wall. The greatest number of these injuries result from automobile accidents in which the chest of the driver is violently crushed against the steering wheel or dashboard or in which pedestrians are struck by rapidly moving vehicles.

Traumatic aortic aneurysms are usually found at the top of the descending aorta just distal to the origin of the left subclavian artery at the site of the ligamentum arteriosum. The other frequent site is in the ascending aorta just distal to the aortic valve.[1] These two points are relatively fixed. Haas[7] has shown that whenever one part of the body is decelerated at a rate which is different from that of another part, the connection between these parts is placed under stress which is proportional to the rates of deceleration. Rice and Wittstruck[8] postulated that the relatively free central portion of the aorta is snapped forward by the retarding force and decelerates at a different rate than the rigidly fixed portions, which decelerate at the same rate as the body as a whole. This difference constitutes a force which is concentrated at the point of maximum fixation. The tears produced are usually horizontal and may involve all layers or only the intima or the intima and media. Rupture of all layers results in sudden death; a tear of the two inner layers may result in a saccular aneurysm; rupture of only the intima may result in a dissecting aneurysm.

The sequence of events in the development of traumatic aortic aneurysm is easily understood and may be demonstrated graphically by serial chest roentgenograms.[4] The initial tear usually results in a mediastinal hemorrhage which produces distortion, irregularity and obscuration of the outline of the aortic arch. The chest roentgenogram shows a "layering" effect around the aortic arch as if the outline of the arch is doubled or tripled by fluid. This finding is not pathognomonic of aortic rupture because such a finding may be present in mediastinitis, perforation of the

Presented at the Scientific Sessions of the Section on Clinical Cardiology of the American Heart Association, Chicago, Ill., April 3, 1954.

From the Departments of Medicine and Surgery, Fitzsimons Army Hospital, and the University of Colorado School of Medicine, Denver, Colo.

esophagus or mediastinal hemorrhage from any source. However, this finding should arouse the suspicion of traumatic aortic rupture when found following severe thoracic trauma, particularly in a patient with shock and evidence of blood loss without visible external bleeding to account for the state of shock. After the initial injury the mediastinal hemorrhage is rapidly absorbed and aneurysmal formation may ensue. Just how long it takes for the aneurysm to form is unknown, but it is probable that only a few weeks are enough. All cases of severe trauma with mediastinal widening and haziness should have repeat chest roentgenograms during the first 2 or 3 months. The aneurysm appears as a mass near the aortic arch and later examinations may show progressive increase in size. Physical examination reveals surprisingly few abnormal findings. Only one of our cases had any signs of cardiovascular abnormality. Fluoroscopy shows a mass that may or may not be pulsatile and cannot be separated from the aorta. The esophagus is displaced to the right and posteriorly. The detection of aneurysm formation indicates that operation should be performed as soon as the condition of the patient permits. The wall of the sac consists of adventitia and fibrous tissue; this should be resected and the laceration of the aortic wall sutured.

Cases seen months or years after their initial injury are usually detected by roentgenograms taken routinely or for some other purpose. All three of our cases were detected in this way. Whether or not surgical therapy is recommended might depend upon five factors: (1) the age of the aneurysm, (2) the size of the aneurysm, (3) evidence of increasing size, (4) the presence of symptoms, and (5) the age of the patient. Any large or increasing aneurysm in a young patient should be treated by resection of the sac and suture of the laceration if possible or by resection of the aneurysm and end-to-end anastomosis or insertion of a homologous aortic graft.

We have recently studied three soldiers who had aneurysms of the descending aorta which were considered to be of traumatic origin. All patients were in their early twenties and none showed evidence of syphilis, arteriosclerosis, coarctation, or arachnodactyly. All suffered severe, nonpenetrating, chest injuries without any evidence of fracture of the bony cage. Chest roentgenograms were considered normal on all prior to injury, whereas after injury all roentgenograms demonstrated shadows which were proven by exploration and/or angiocardiography to be aneurysms of the descending aorta.

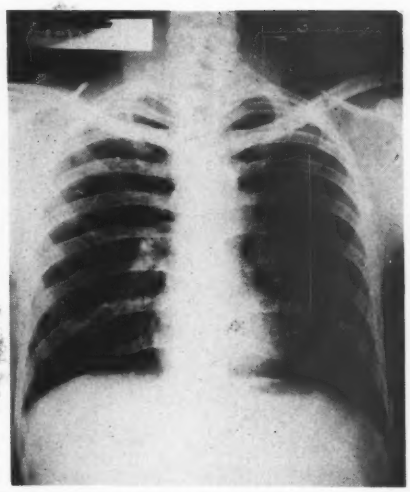


FIG. 1 Case 1. Posteroanterior chest x-ray film showing aneurysm at top of descending aorta.

CASE REPORTS

Case 1. A 22 year old soldier was injured in an automobile accident on Jan. 1, 1950, when the car he was driving collided head-on with another vehicle. He was hospitalized with the complaint of left chest pain. Physical examination revealed minor bruises of the chest wall, no fractures, and no evidence of shock. Chest roentgenograms showed a right hemothorax, fluid in the left costophrenic angle and no evidence of fracture of the bony thorax. He was discharged on the eighth day and remained well. A routine chest x-ray study two years later showed a left posterior-superior mediastinal mass which on fluoroscopy could not be separated from the aorta and which did not appear to pulsate (fig. 1). He was transferred to our hospital for diagnosis and treatment. Physical examination was normal and laboratory studies, including serologic tests were negative. He underwent exploratory thoracotomy with a preoperative diagnosis of posterior gutter tumor. Thoracotomy revealed an aneurysm of the aorta. The chest was closed without any definitive treatment. Subsequent follow-up films have not shown any detectable enlargement.

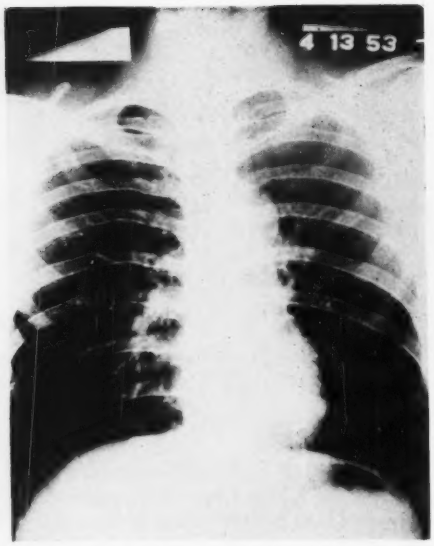


FIG. 2 Case 2. Posteroanterior chest x-ray film showing aneurysm at top of descending aorta.

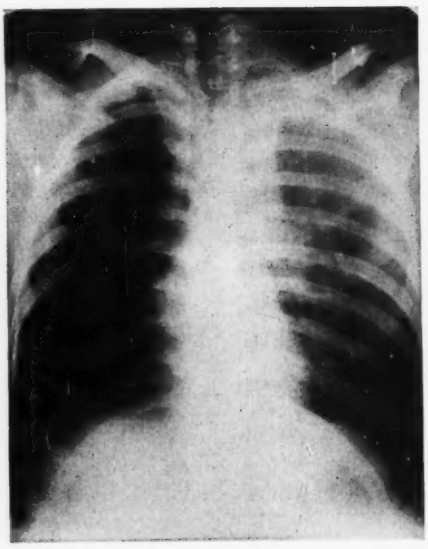


FIG. 3 Case 3. Posteroanterior chest x-ray film at time of injury, showing widening of superior mediastinum and a hazy left lung field.

Case 2. A 20 year old soldier was injured in Paris in May 1945, when his jeep collided with the back of a parked trailer truck; he was unconscious after injury for 72 hours. Physical examination showed only a fractured jaw. Chest x-ray films made at that time were considered negative but are not available. After regaining consciousness he complained of pain in the jaw and in the chest. Eight days after injury he felt dizzy, fainted and fell to the floor. No particular significance was attached to this episode at the time and the observations on the blood pressure and pulse during this period are lacking. He soon became asymptomatic and was discharged to duty. A routine roentgenogram eight months later showed mediastinal widening. In March 1953, another routine roentgenogram showed further slight enlargement of the mass with a layer of calcification in the lower lateral border (fig. 2). Physical examination was normal and routine laboratory studies, including serologic tests, were negative. Fluoroscopy showed a pulsating mass which could not be separated from the aorta. Angiocardiography showed the mass to be an aneurysm of the descending aorta. Operative intervention was not recommended because of the age of the aneurysm and the presence of calcium in the wall which made repair hazardous.

Case 3. A 23 year old soldier was injured in an automobile accident on Dec. 11, 1952, in Okinawa. He was hospitalized within two hours at which time he was in moderate shock. The blood pressure was 70/20 and the pulse rate 120 per minute. The patient was slightly cyanotic. Physical examination was otherwise normal. A blood count showed 3.5 million erythrocytes per cubic milliliter, hematocrit of 31 per cent, and hemoglobin of 10 Gm. per 100cc. A chest roentgenogram was negative for rib fracture but showed a left hilar and superior mediastinal haziness (fig. 3). Two blood transfusions, each of 500cc., were given with alleviation of his shock and the unexplained anemia. He was discharged asymptomatic two weeks after injury. A routine chest roentgenogram three months later showed a large mass in the left mediastinum (fig. 4), for which he was transferred to our hospital in April 1953. Physical examination was normal except for the presence of a tracheal tug and a grade II systolic murmur audible over the base and in the interscapular area posteriorly. Routine laboratory studies, including serologic tests, were negative. Fluoroscopy showed a large pulsatile mass which could not be separated from the aorta and displaced the esophagus to the right and posteriorly. Angiocardiography showed an 8 by 9 cm. aneurysm of the descending aorta (fig. 5).

On June 27, 1953, the chest was explored and the large aneurysm isolated. The aorta was occluded above and below the aneurysm and the sac opened. Instead of the usual narrow, slit-like opening, the entire anterior wall of the aorta had disappeared. Two rings of tissue marking the torn aortic ends had retracted and become everted so that both orifices faced anteriorly. Normal yellow colored intima stop-

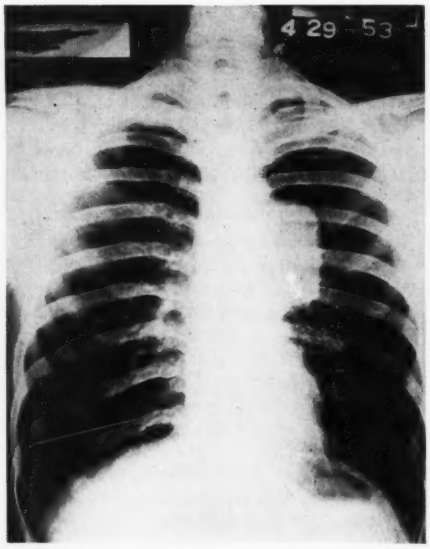


FIG. 4 Case 3. Posteroanterior chest x-ray film made four and one-half months later, showing a large aneurysm at the top of the descending aorta.

FIG. 5 Case 3. Angiocardiogram showing the large aneurysm.

ped sharply at these rings. The tear involved more than half of the circumference of the aorta and extended through the intima and media so the wall of the aneurysm was formed by adventitia and fibrous tissue. Potts clamps were placed at the base of the sac, reducing the lumen of the aorta to normal size. Excision of the excess sac was followed by suture of the edges. Sclerosing polythene was placed about the aneurysmorrhaphy site. Later that day he developed signs of aortic block so he was operated upon again. The repaired aorta contained a firm clot which was evacuated and resutured and regional heparinization was instituted. This was followed by prolonged systemic anticoagulant therapy. Postoperatively he showed slow but progressive diminution of the femoral pulses. Postoperative angiocardiograms showed that the repaired aorta was tortuous, displaced forward and irregular. He was allowed to go on convalescent leave and while at home, on Sept. 2, 1953, he suffered a hemoptysis of 1,000cc. He was hospitalized elsewhere and 10 days later he experienced a final fatal hemorrhage. Autopsy showed that the middle of the suture line had ruptured into a bronchus to the left upper lobe. We believe that our failure resulted from placing our sutures in the sac wall rather than in good aortic tissue.

SUMMARY

Aneurysm of the thoracic aorta may follow nonpenetrating injuries of the thorax unaccompanied by rib fractures or even obvious bruising of the chest wall. Long-term survivals thereafter are possible but not the rule. The aneurysms characteristically appear in the first portion of the descending aorta or less commonly in the proximal ascending aorta. At first there is only widening and obscuration of the aortic arch, but later definite aneurysm may ensue. A large aneurysm, progressive enlargement, or symptoms may necessitate excision or repair. Such repair is now feasible. If all the layers of the aortic wall cannot be sutured, excision of the sac with homologous graft should be performed. Traumatic aortic aneurysm should be considered in the differential diagnosis of obscure lesions in the thorax when there is a history of severe antecedent trauma.

SUMARIO ESPAÑOL

Aneurisma de la aorta torácica puede ser producido por traumatismo no penetrante del tórax sin acompañamiento de fracturas de costilla o aún de sencillas contusiones de la pared torácica. Supervivencia por largo tiempo luego es posible pero no la regla. Las aneurismas caracteristicamente aparecen en la primera

porción de la aorta descendente o menos comunmente en la porción proximal ascendente. Al principio solamente ocurre obscurecimiento del arco aórtico, pero más tarde un aneurisma puede aparecer. Un aneurisma grande, ensanchamiento progresivo, o los síntomas, pueden hacer necesario la excisión o corrección quirúrgica. Tal reparación es hoy posible. Si todas las capas de la pared aórtica no pueden ser suturadas, excisión del saco con un injerto homólogo puede intentarse. Aneurisma aórtico traumático debe ser considerado en el diagnóstico diferencial de lesiones obscuras en el tórax cuando hay un historial de trauma antecedente.

REFERENCES

[1] Strassmann, G.: Traumatic rupture of the aorta. Am. Heart J. **33:** 508, 1947.

[2] Hollingsworth, R. K., Johnston, W. W., and McGooey, J. F.: Traumatic saccular aneurysm of the thoracic aorta. J. Thoracic Surg. **24:** 325, 1952.

[3] Kastl, W. H.: Traumatic rupture of the thoracic aorta. Ann. Surg. **137:** 111, 1953.

[4] Wyman, A. C.: Roentgenologic diagnosis of traumatic rupture of the thoracic aorta. Arch. Surg. **66:** 656, 1953.

[5] Bahnson, H. T.: Definitive treatment of saccular aneurysms of the aorta with excision of the sac and aortic suture. Surg., Gynec. & Obst. **96:** 383, 1953.

[6] Johnston, J. B., Kirklin, J. W., and Brandenburg, R. O.: The treatment of saccular aneurysms of the thoracic aorta. Proc. Staff Meet., Mayo Clin. **28:** 723, 1953.

[7] Haas, G. M.: Types of internal injuries of personnel involved in aircraft accidents. J. Aviation Med. **15:** 77, 1944.

[8] Rice, W. G., and Wittstruck, K. P.: Acute hypertension and delayed traumatic rupture of the aorta. J.A.M.A. **147:** 915, 1952.

"Isolated" T-Wave Negativity in the "Ischemic Phase" of Myocardial Infarction in Man

By ROBERT C. SCHLANT, M.D., HAROLD D. LEVINE, M.D., AND C. CABELL BAILEY, M.D.

T-wave inversion, in leads localized to a small segment of the precordium, has in rare instances been described as a normal variant. The present report concerns a number of individuals in whom more or less similar T-wave changes developed under circumstances suggesting myocardial ischemia, and who went on to develop acute infarction of the anterior wall of the heart. This may be a clinical analogue of the brief T-wave inversion which has been observed early in experimental coronary artery compression.

INVERSION of the T wave has been described as the immediate consequence of experimental ligation of the descending branch of the left coronary artery.[1-3] It is only on more prolonged occlusion that changes develop in the RS-T segment or in the QRS complex. In acute coronary thrombosis in man, by contrast, an elevation of the RS-T segment is generally the earliest change recorded. This may be associated with or followed by terminal inversion of the T wave or by the development of an inverted U wave. It may likewise accompany or precede changes in the QRS complex. The possibility that inversion of T waves might occur as an isolated finding in the earliest stages of acute clinical myocardial infarction has frequently been suggested or inferred but never convincingly demonstrated. Most of the publications appearing in the last decade or two on the "impending,"[4, 5] "preliminary,"[6] "premonitory"[7-9] or "formative"[10] stages of myocardial infarction were written when only the three conventional leads and one,[5, 6, 7, 11] two[4] or three[8, 12] chest leads were recorded. These showed no changes at all[4, 7] or instability of the T waves[5, 6, 8-13] which was difficult or impossible to localize or evaluate because of what most electrocardiographers now consider inadequate electrocardiographic exploration. Yater and his co-workers[11] considered a "premonitory" phase of acute coronary artery occlusion as too vague and intangible a subject to deserve discussion; they pointed out that any anginal form of attack, except in established cases of angina pectoris, should be considered premonitory until proved otherwise. It has been noted moreover that in rare clinical instances of acute myocardial infarction associated with fever, leukocytosis or elevation of the sedimentation rate, the electrocardiogram may reveal only the development of deeply inverted T waves[14, 15] in all precordial leads.

It is the purpose of this paper to present six patients who may be considered as having been adequately explored, who demonstrated a possible early "ischemic" phase of acute anteroseptal myocardial infarction, and a seventh patient in whom the electrocardiogram reverted to normal. In these cases the T-wave inversion was "isolated" in two senses: namely in the temporal sense that they preceded the development of alterations in the RS-T segment and/or the QRS complex, or never progressed beyond the T-wave phase, and in the topographic sense that in this early "T-wave" phase the changes were prominent in one or two of the midprecordial leads, such as leads V_3 and V_4 or leads V_2 and V_3, while the flanking leads showed these changes to a much lesser extent (cases 2, 3 and 5) or not at all (cases 1, 4, 6, 7). Five of the patients were on the wards of the Peter Bent Brigham Hospital, one at the New England Deaconess Hospital and one was seen in the private practice of one of us (H.D.L.). None of the patients received digitalis prior to or during hospitalization.

From the Medical Clinic, Peter Bent Brigham Hospital, the Department of Medicine, Harvard Medical School, and New England Deaconess Hospital, Boston, Mass.

Case 1. D. N. (P.B.B.H. 7E739), a 54 year old construction worker, had had severe kyphoscoliosis with mild dyspnea on exertion following an injury at the age of 6 months. There were no other cardiac symptoms until one month before admission when he began to suffer from angina pectoris. This became progressively more frequent and severe. Two weeks before admission one episode lasted two hours and required morphine for relief. Following this he was treated in another hospital where electrocardiograms were not remarkable, and reoentgen examination showed his gall bladder and gastrointestinal tract to be normal. He was discharged from that hospital five days before admission to Peter Bent Brigham Hospital. His angina pectoris, however, rapidly became almost completely incapacitating with very little relief from nitroglycerin, and he was admitted to the Peter Bent Brigham Hospital on Nov. 24, 1952.

The patient was a short, severely deformed man who had a typical attack of angina pectoris during the admission examination. He had a marked dorsal kyphoscoliosis with the convexity to the right. The blood pressure was 120/80 and the pulse rate 70. There were a few moist rales at the left base which disappeared a few hours after admission. There was no other evidence of congestive failure. The heart was apparently moderately enlarged, but the chest deformity made the evaluation of heart size difficult. The heart sounds were of good quality. There was no murmur, gallop rhythm or friction rub. The remainder of the physical examination was not remarkable. Electrocardiograms on admission (fig. 1*A*) showed predominantly inverted T waves in leads V_3 and V_4 with upright T waves in the flanking leads. These suggested myocardial ischemia, but were possibly a normal variant.[16] A tracing the next day was essentially unchanged in the usual 12 leads. Precordial exploration[16, 17] showed the area of T-wave inversion to extend into the third left intercostal space at the vertical levels of V_5 and V_6 but not into the accessible second intercostal space. Exploration was not car-

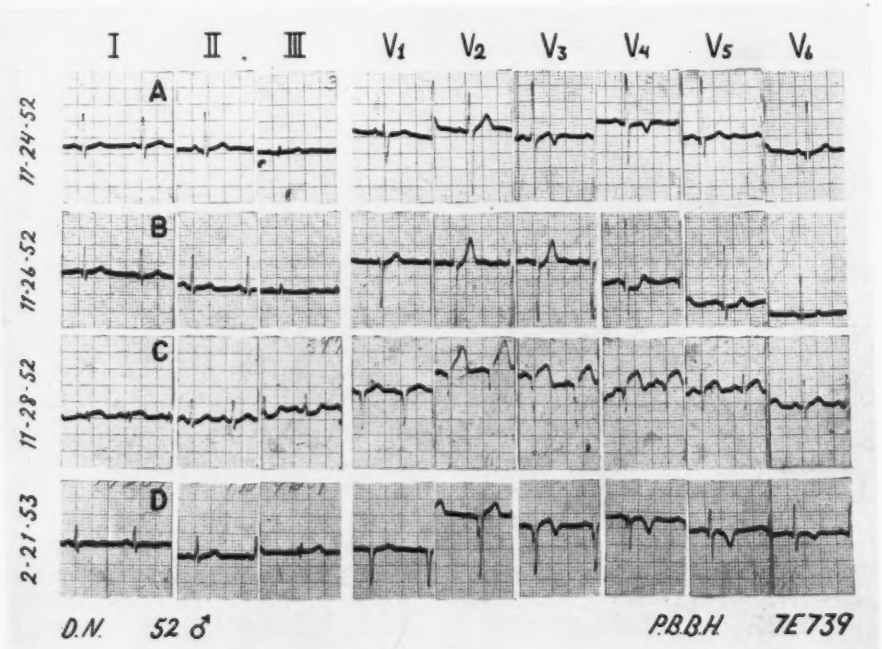


FIG. 1. *Isolated T-wave negativity as prelude to acute transmural antero-septal infarct.* The patient was a 54 year old man with kyphoscoliosis. Angina pectoris had been present for one month, increasing in frequency and severity. Previous electrocardiograms were normal. Initial tracings recorded on day of admission show biphasic T in lead V_3, inverted T in lead V_4. The Q-T interval is normal. No laboratory evidence of tissue breakdown (*A*). The second set of tracings (11/26/52) shows slightly depressed RS-T segments in leads V_3, V_4 and V_5 (*B*) compatible with subendocardial ischemia. The third series of curves (11/28/52) shows diagnostic changes of acute anteroseptal infarction (*C*). The Q-T interval is normal. At this time the patient had fever and leukocytosis. The final set of tracings three months later shows residual changes of anteroseptal infarction (*D*).

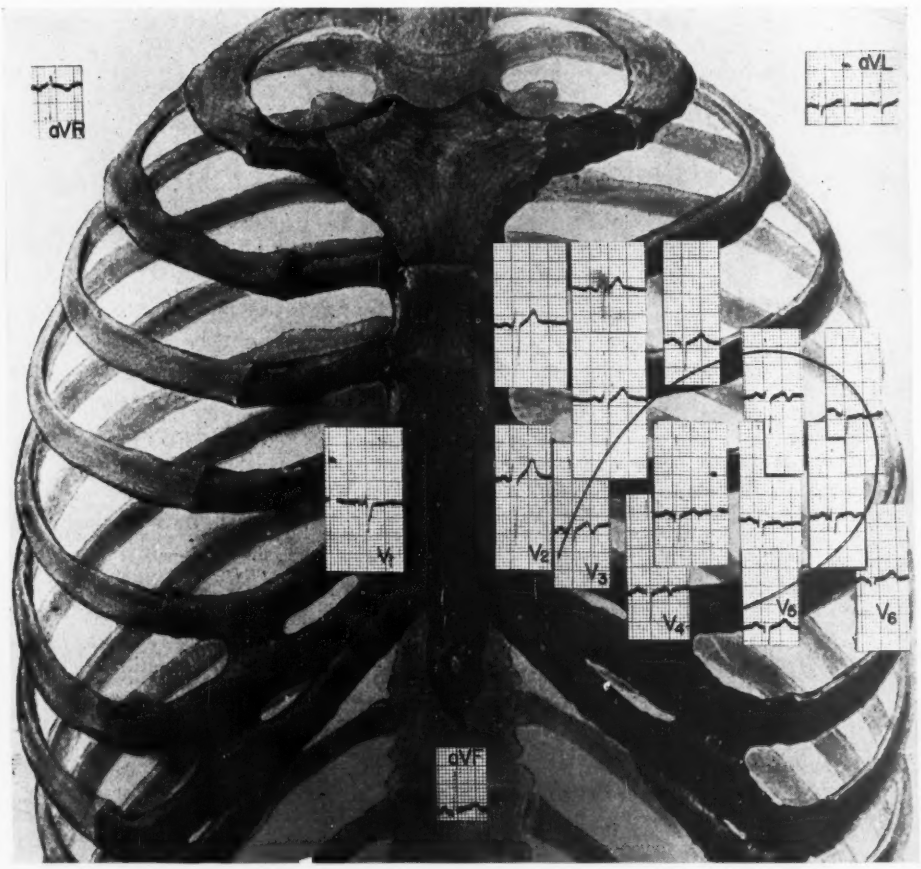


FIG. 2. *Topographic exploration of precordium in the same patient on 11/25/52.* The area of T-wave negativity involves leads V_3 and V_4 in the usual six precordial leads, and extends to the vertical level of V_4, V_5 and V_6 in the fourth intercostal space and V_4 in the third intercostal space. The T wave is almost flat at the vertical level of V_5 in the third intercostal space but upright in the entire accessible portion of the second intercostal space and in lead aV_L. Exploration of the lower precordium is incomplete.

ried out inferiorly but the T waves were upright in leads aV_L and aV_F (fig. 2). These changes were interpreted as representing localized ischemia. On Nov. 26, 1952 (fig. 1*B*), tracings suggested subendocardial ischemia.

Leukocytosis (11,300) and fever (101 F. rectally) did not develop until Nov. 28, 1952, the day when decisive electrocardiographic evidence of acute transmural anteroseptal myocardial infarction was first recorded (fig. 1*C*), and the sedimentation rate did not rise until five days later. The patient was treated with the chair and bed program, sedatives and anticoagulants and received nitroglycerin and narcotics for pain. During the first four days he continued to have frequent, moderately severe episodes of chest pain. Then, coincident with the appearance of definite electrocardiographic evidence of infarction, the pain disappeared. It recurred in a much less severe form 10 days later. Tracings on December 3, 9, 11 and January 14 demonstrated the usual sequence of RS-T segment elevation followed by a return to the base line with the development of terminal T-wave inversion, still present in the final tracing taken Feb. 21, 1953 (fig. 1*D*). Since discharge on Dec. 22, 1952, his course has been uneventful, although he still has occasional mild angina pectoris.

Case 2. L. J. (P.B.B.H.), a 61 year old widow, had had rare episodes of angina pectoris for several years, hypertension for four years and a pulsating

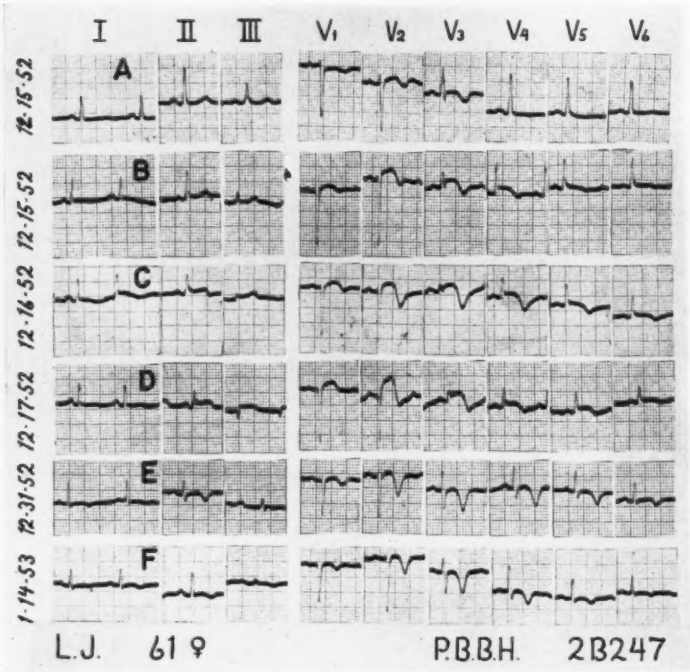


FIG. 3. *T-wave negativity most pronounced in leads V_2 and V_3 briefly preceding acute anteroseptal infarction.* The patient was a 61 year old woman with angina pectoris, hypertension and thrombosed abdominal aneurysm. There had been four prolonged attacks in the 18 days before admission. The patient suffered eight hours of precordial pain. The initial electrocardiograms (12/15/52) show inversion of T waves in leads V_1 through V_5, most pronounced in lead V_3 (*A*). The T waves are flat in V_4 and V_5. The Q-T interval is prolonged by 18 per cent. The patient had fever at this time but no laboratory evidence of tissue breakdown. The second set of tracings recorded later that day (*B*) shows elevation of RS-T segments and late inversion of T waves in leads V_1 through V_6. In conjunction with the clinical story these changes justified a clinical diagnosis of acute myocardial infarction. The third set recorded the following day (12/16/52) shows diagnostic evidence of acute anteroseptal infarction (*C*). The Q-T interval is prolonged 40 per cent ("postischemic" T waves). The next two sets (12/17 and 12/31) show characteristic sequential changes (*D*, and *E*) while the final set (1/14/53) shows no decisive residual changes of infarction (*F*). At this time T waves were inverted everywhere but maximally in lead V_3.

upper abdominal mass for one year. Eighteen days before admission while walking she developed an epigastric pain similar to her angina pectoris but lasting an hour before subsiding spontaneously. She had three similar but milder attacks in the week preceding admission; then on Dec. 15, 1952, she was awakened by severe knife-like precordial pain, radiating to her left shoulder and arm but also spreading into the left upper quadrant of her abdomen. The pain persisted in somewhat milder form until she was admitted eight hours later.

When first seen she was in acute pain, clutching at her chest and upper abdomen. The blood pressure was 170/100 and the pulse rate 106. The heart was not enlarged and no murmur, gallop rhythm or friction rub was heard. There was no respiratory distress, increased venous distention or edema, but a few rales were heard at the left lung base. There was a pulsating mass in the left upper quadrant of the abdomen, measuring 5 or 6 cm. in diameter. Roentgen-ray examination showed it to be an abdominal aneurysm with calcification in its wall. Laboratory studies showed a persistent trace of albumin in her urine. Her sedimentation rate on admission was 7 mm. in 1 hour; this soon rose to 37 mm. in 1 hour.

The electrocardiographic sequence is illustrated in figure 3 and described at length in the legend. Here again localized T-wave inversion gave way rapidly to characteristic changes of acute anteroseptal infarction.

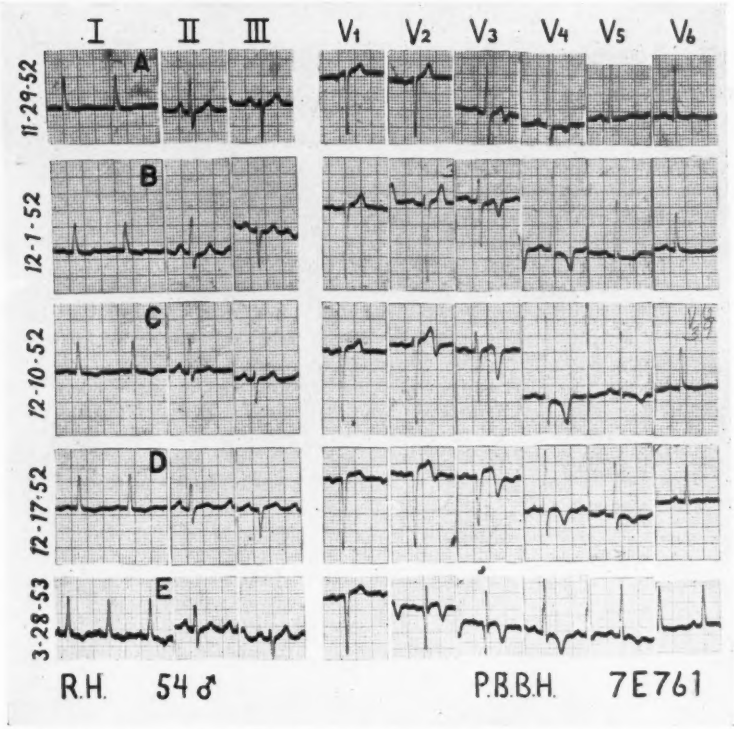


FIG. 4. *Isolated "ischemic" T waves followed in two and one-half weeks by decisive changes of acute anteroseptal infarct.* The patient was a 54 year old man with angina pectoris for nine months; the angina had been more frequent recently but was always promptly relieved by nitroglycerin. Three-fourths hour of chest pain brought the patient to the hospital. The initial set of tracings (11/29/52) shows inversion of T in lead V_4, clearly biphasic (+−) T waves in lead V_3 and slightly biphasic T waves in lead V_5 (*A*). The Q-T interval at this time is shortened to 10 per cent below expected normal ("ischemic" T waves). The second set (12/1/52) shows more deeply inverted T waves in leads V_3 and V_4 (*B*). On 12/10/52 the inversion of T waves is even more pronounced and widespread but evidence of infarction is still lacking (*C*). On 12/17/52 the R waves have disappeared in leads V_1 and V_2, are minuscule in lead V_3, and the tracings are diagnostic of acute anteroseptal infarction (*D*). The Q-T interval is lengthened by 20 per cent ("postischemic" T waves). The tracings three months later show residual evidence of old anteroseptal infarct with inverted T waves (*E*).

For the first two days the patient had an elevation of her temperature, pulse and respiratory rates. Her blood pressure gradually fell to 100/80 18 hours after admission, then slowly rose to 140/80 on discharge. The chest pain was controlled with morphine. It was noted that the abdominal aneurysm remained tender and that very slight pressure over it reproduced the pain in her upper abdomen and at times in the substernal area. She suffered no recurrence of precordial pain radiating to her shoulder or arm. She had an occasional episode of upper abdominal pain, not radiating to the precordium. On Jan. 26, 1953, aortography showed that the sac of the aneurysm was already lined with a solid thrombus and no surgical treatment was recommended. Since discharge on Jan. 30, 1953, she has continued to have occasional episodes of upper abdominal pain in addition to infrequent episodes of angina pectoris which she considers distinctly different from the abdominal pain. Her blood pressure has returned to former levels.

Case 3. R. H. (P.B.B.H., 7E761*), a 54 year old man, was well until nine months before admission when he first developed typical angina pectoris. This always abated within five minutes on resting. For three weeks prior to admission this had occurred

* We are indebted to Dr. A. W. Contratto for permission to use this case and for two of the electrocardiograms reproduced.

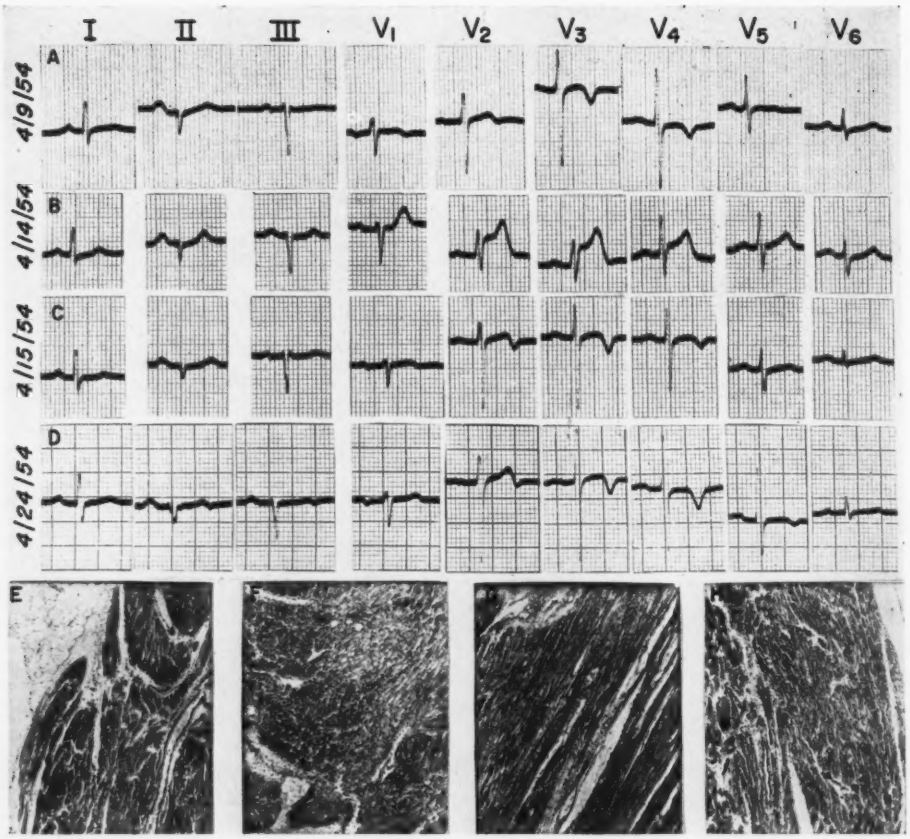


FIG. 5. *Protracted isolated T-wave negativity with brief transient RS-T segment elevation associated with intramural myocardial infarction.* Case 4, M. A., was a 47 year old man with angina pectoris. Initial tracings show inversion of T waves limited to leads V_3 and V_4 (*A*). Tracings recorded the following day with additional precordial leads are shown in figure 6. Daily tracings showed no change until 4/14/54 when the T-wave inversion gave way to RS-T segment elevation in leads V_2, V_3 and V_4 (*B*). The expected subsequent progression failed to develop. Instead tracings continued essentially unchanged over those recorded on admission (*C* and *D*). The patient died two days after the last tracing. Postmortem examination showed recent intramural infarction at the apex of the left ventricle. The left photomicrograph showed normal subepicardial (*E*) and the right photomicrograph normal subendocardial myocardium (*H*). The two intervening sections (*F* and *G*) show portions of isolated and conglomerate intramural necroses. The third section shows necrotic and infiltrated muscle bordering on intact muscle layers. (×90)

more frequently. On the morning of admission, while on the way to his physician, he noted the onset of a similar pain which lasted 45 minutes and was relieved by nitroglycerin. He was then admitted on Nov. 29, 1952.

When seen in the hospital a few hours after the subsidence of pain, he was in no acute distress and physical examination was not remarkable. The blood pressure was 125/80 and showed no significant fall throughout the hospitalization. There was no fever, leukocytosis or elevation of the sedimentation rate. In the absence at that time of definite evidence for the diagnosis of myocardial infarction, but with the purpose actually of preventing myocardial infarction, he was treated with anticoagulants. During the first two weeks he required occasional nitroglycerin for chest distress; thereafter he had angina pectoris only rarely, he recovered uneventfully but still has an occasional episode of angina pectoris.

The electrocardiographic sequence is illustrated in figure 4 and described in the legend. It was shortly after the episode of severe pain that the tracings

showed localized inversion of the T waves, but it was not until the passage of another 19 days that the tracings showed diagnostic evidence of infarction.

Case 4. M. A., a 47 year old dye-worker, had noted over a six-week period epigastric and substernal distress on walking two blocks or more, relieved by stopping, and occasionally associated with a sense of gaseous distention which at times was relieved by belching. He was admitted on April 8, 1954. Except for his sthenic habitus examination was negative. The important laboratory findings were the white blood cell counts and the corrected sedimentation rates recorded on the following dates respectively: April 8, 10,000 and 16 mm., April 9, 15,300 and 22 mm., April 10, 12,000 and 31 mm., April 12, 8800 and 32 mm., and April 20, 6200 and 33 mm. An electrocardiogram on April 9 (fig. 5*A*) showed T-wave inversion limited to leads V_3 to V_4. On the following day, April 10, 1954, extensive exploration of the precordium (fig. 6) showed that the area of dispersion of this T-wave inversion was quite widespread, thus contrasting with the rather limited distribution of this change when it is encountered as a normal variation[16, 17] or as observed in case 1.

A transient pronounced degree of RS-T segment elevation was recorded on April 14 (fig. 5*B*), but this disappeared on the following day (fig. 5*C*) and the tracings remained substantially unchanged (fig. 5*D*) over those recorded on admission until his sudden demise on April 26. During the earlier part of his hospitalization he had frequent pains in both arms lasting from 10 minutes to an hour or so and relieved by nitroglycerin. He had been quite free of pain during the last week of his life, until the night before his death when it returned with unrelenting severity. Postmortem examination showed a recent thrombus in the descending branch of the left coronary artery. There was also a fairly recent intramural infarct in the region of the apex of the left ventricle (fig. 5*F* and *G*). There was no evidence

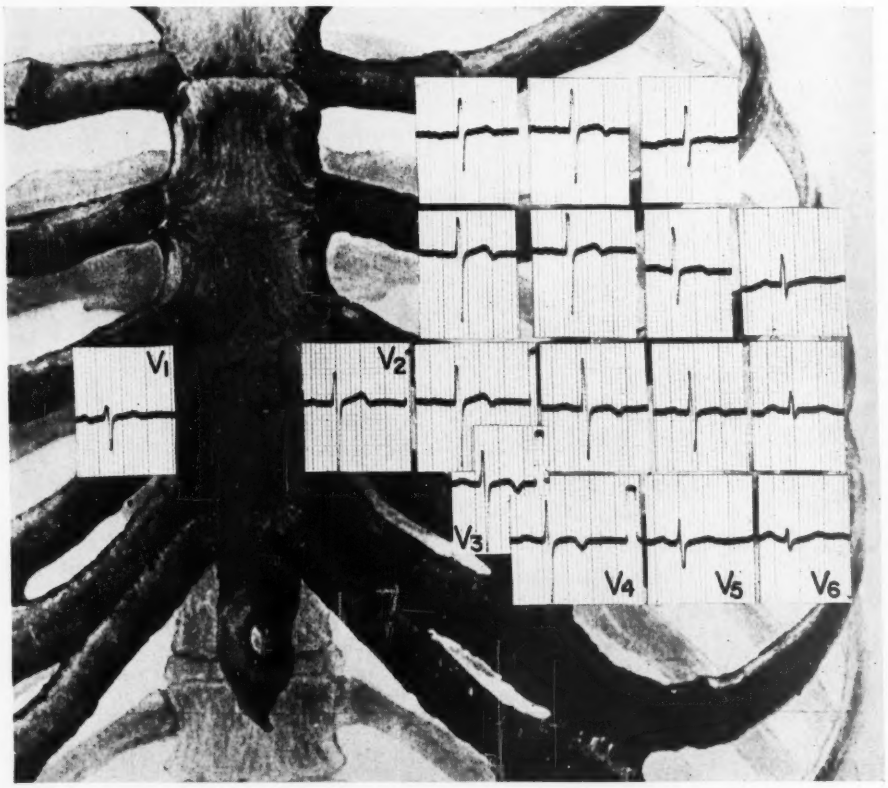


FIG. 6. *Topographic exploration of precordium in same patient on 4/10/54.* This is "apparent" isolated T-wave negativity in that the T wave inversion in leads V_3 and V_4 is clearly an extension from above into the line of the usual six leads of a large area of T-wave negativity. It is, therefore, not the very closely circumscribed, paradoxic and benign "isolated T-wave negativity" of Grant.

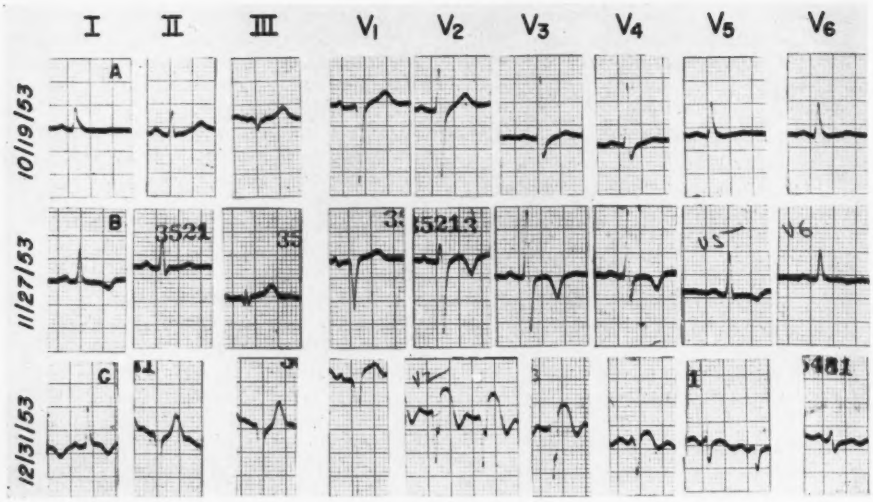


FIG. 7. *T-wave inversion over midprecordium protracted over three-week period of angina decubitus preliminary to acute anteroseptal infarction.* Case 5, J.F.S., was a 45 year old diabetic with an old myocardial infarct one year, and angina decubitus beginning two months, before initial electrocardiograms (*A*) which showed low or flat T waves. The patient admitted with exacerbation of angina two weeks before the second tracing (11/27/53) which, for the first time, showed T-wave inversion over a large part of the precordium but with upright T-waves in V_1 and flat T-waves in V_6 (*B*). These changes persisted throughout the remainder of hospitalization. The third set of tracings was recorded on readmission (12/31/53) for a classic episode of acute anteroseptal infarction (*C*).

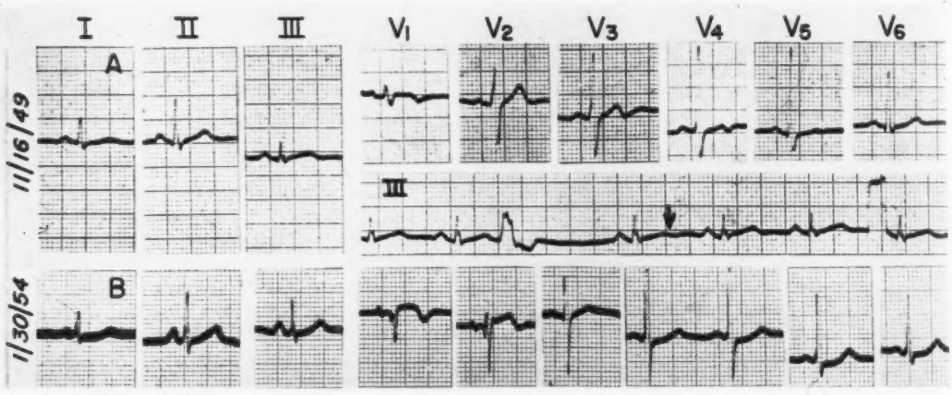


FIG. 8. *Isolated T-wave inversion persistent over five-year period.* Case 6, F.S., was a 52 year old physician with angina pectoris for eight years. Repeated tracings from 1949 to 1954 showed isolated T-wave inversion in leads V_3, V_4 and V_5 (*A*). At the time of the original tracing the T wave of a post-extrasystolic beat was lowered (see arrow), suggestive evidence for myocardial ischemia. In January 1954, the patient suffered a mild anteroseptal infarction (*B*).

whatever of extension of the infarct to the epicardial (fig. 5*E*) or endocardial surface (fig. 5*H*).

Case 5. J. F. S., a 45-year old undertaker with diabetes mellitus of 27 years' duration, suffered a myocardial infarction in November 1944, with good recovery. In October 1953, his electrocardiogram (fig. 7*A*) was normal except for low to flat T waves. In early August 1953, he had begun to have intermittent epigastric or low substernal pain, nonradiating, lasting from one to four minutes, never related to exertion, but at times precipitated by emotional tension. He frequently awoke from a dreamless sleep with pain which improved when he sat upright.

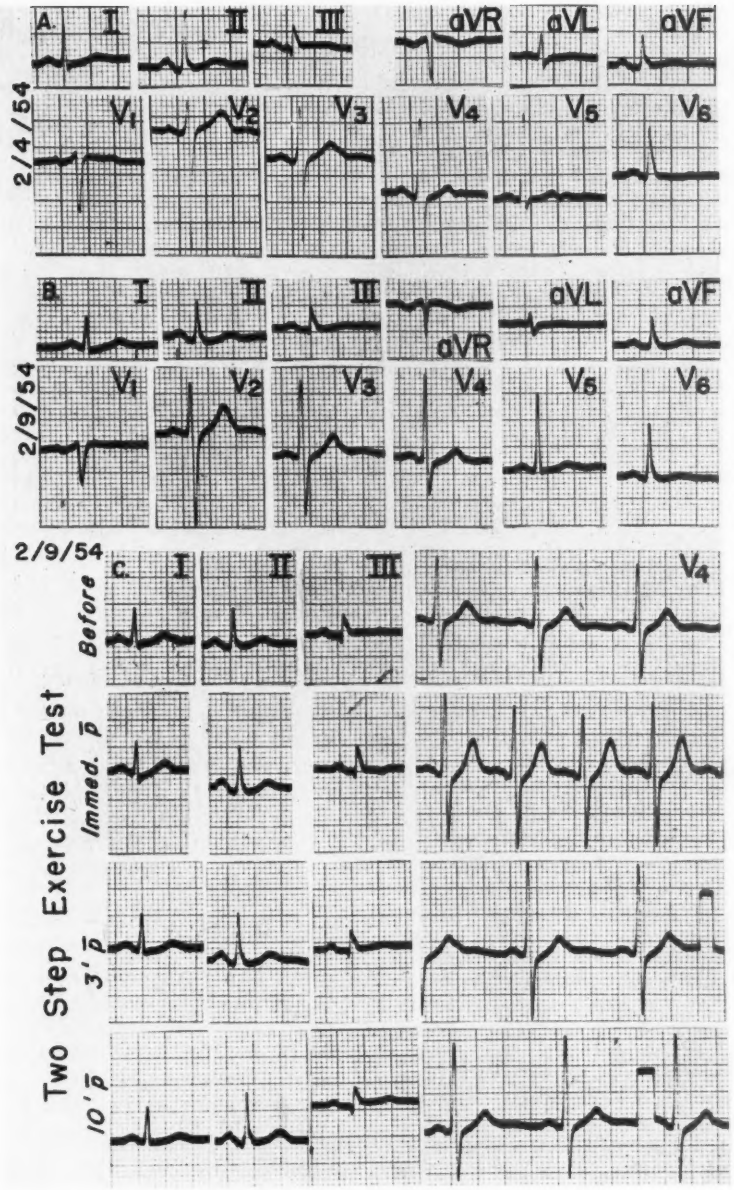


FIG. 9. *Transient localized notching of T waves followed by "positive" Master test.* Case 7, M.K., was a 44 year old man with a sense of constriction in throat. A tracing on 2/4/54 shows notching of T in V_4 and V_5 (*A*). Five days later these changes have disappeared (*B*), but a two-step exercise test brings out changes distinctive of acute coronary insufficiency (*C*), presumptive evidence that the earlier changes were likewise ischemic in nature.

Nitroglycerin usually gave relief after producing an initial exacerbation of the pain. The pain became so much more frequent and severe that the patient was admitted to the New England Deaconess Hospital on November 13, 1953. Gastrointestinal studies were normal. The white blood cell count was normal on admission, rose to 12,300 on November 19 and to 12,500 on November 20; it fell to 8200 on November

21. The sedimentation rate remained normal during his hospital stay and he was afebrile throughout. An electrocardiogram recorded during severe spontaneous pain showed pronounced RS-T segment depressions typical of "subendocardial ischemia" but these displacements disappeared when he was free of pain. In comparison with the original tracings (fig. 7*A*) the electrocardiograms showed no alterations until November 27, when they showed striking inversion of the T waves in leads V_2, V_3, V_4 and V_5, most pronounced in lead V_3 (fig. 7*B*). T was upright in lead V_1 and flat in lead V_6. During the remainder of his hospitalization the electrocardiograms showed no important changes, never developing RS-T or QRS changes in spite of persistent angina pectoris. At the time of his discharge on December 18 he was having only an occasional attack of chest pain. He was readmitted on Dec. 30, 1953, in a fullfledged attack of acute anteroseptal infarction. The electrocardiogram now showed diagnostic changes (fig. 7*C*) and the white blood cell count rose to 25,300. He had a much more comfortable time of it in this second admission and was discharged improved on Feb. 18, 1954. He died suddenly in mid-June 1954, five days after an attack of chest pain unassociated with electrocardiographic or other laboratory evidence of myocardial infarction. Permission for postmortem examination was not granted.

Case 6. F. S., a 52 year old physician, had noted substernal pain on walking against a cold wind during the past eight years. In 1949, an electrocardiogram, made in connection with a survey conducted by the United States Public Health Service showed T-wave inversion localized to leads V_3 and V_4 (fig. 8*A*). For two weeks he suffered from what we have chosen to call "paroxysmal nocturnal angina," a type of angina decubitus which would wake the patient from his sleep and which would be relieved by sitting upright in bed. Later the night pain was not thus relieved and he had prolonged pain during the day. On admission (Jan. 29, 1954), his white blood cell count was 12,400. His corrected sedimentation rate rose to a high of 27 mm. in 1 hour on Feb. 1, 1954, and during the first 36 hours of hospitalization he had a slight fever (maximal temperature 100.8 F.). For a few days he continued to have episodes of pain promptly relieved by nitroglycerin and on one occasion by right carotid sinus stimulation which at the same time produced cardiac arrest lasting seven seconds. Electrocardiograms (fig. 8*B*) showed initial and sequential changes characteristic of acute anteroseptal infarction from which he made a satisfactory recovery.

Case 7. M. K., a 44 year old man, consulted an otolaryngologist because of a choking feeling in the throat occurring after meals, at rest or during work. He was referred for an electrocardiogram which showed notching with minimal inversion of the T waves in leads V_4 and V_5 and flat T waves in lead V_6 on March 4, 1954 (fig. 9*A*). Repeat tracings recorded five days later were within normal limits (fig. 9*B*), but a Master two-step exercise test at that time (fig. 9*C*) induced changes characteristic of acute coronary insufficiency.

Although we know of no long-term observations regarding the localized T-wave inversions described by Grant and his coworkers (16) as a normal variant, it would, we believe, be expected to remain a fixed feature of the electrocardiogram. In this case, by contrast, the disappearance of the localized T-wave changes would appear to make them doubly significant. The latency of "ischemic" changes was then demonstrated by the "positive" two-step test. In this connection it is of interest that, whereas the spontaneous change consisted of notching of the T wave, the induced change consisted of RS-T segment depression. This experience is similar to that in case 5 (J.F.S.) in which RS-T segment depression was induced by the two-step test and was recorded in much greater degree during a spontaneous episode of pain, though the subsequent spontaneous development was the evolution of profound T-wave inversion.

In the clinic, then, it appears that these early T-wave changes, whether or not associated with evidence of tissue breakdown, may progress through the stages of RS-T and QRS changes after a short (cases 1, 2 and 3) or longer (cases 5 and 6) interval; they may progress to the stage of RS-T segment shift and, rather than proceed to develop more definitive changes of myocardial infarction, actually recede to the stage of pure T-wave inversion (case 4); or they may retrogress from a phase of T-wave inversion to a normal electrocardiogram (case 7).

Discussion

The early ischemic changes recorded by Bayley in dogs were present for only a matter of seconds or minutes. It has been suggested that, if similar electrical changes actually occur clinically in man, it is extremely unlikely that they would be recorded, since the patient simply does not present himself to the physician during the first few moments of an acute coronary thrombosis. The observations of Graham and Laforet[19] on accidental coronary artery ligation in man probably come as near to the experimental set-up of Bayley as we are likely to come; one of these showed T-wave negativity, the other increased T-wave posi-

tivity. The first patient described by Roesler and Dressler[20] showed transient inversion of T in lead V_3 during the subsidence of a spontaneous attack of angina pectoris at the height of which RS-T segment elevations had been recorded. Is it possible that the changes, which are induced in the dog over a minute or so by deliberate ligature, may develop spontaneously in man over the course of hours or days? If the process of closure, whatever its precise mechanism, were slow and progressive, it seems conceivable that such changes might indeed be recorded clinically. In the present group of cases the interval between the known presence of T-wave inversion and the development of electrocardiographic alterations diagnostic of acute myocardial infarction was 4 days in the first case, 10 hours in the second, 19 days in the third, 34 days in the fifth, and 5 years in the sixth case. In the fourth case there was a five-day interval between the T wave inversion and RS-T segment elevation which then disappeared. And in the seventh case the T-wave inversion disappeared and more profound changes never developed. In some of those cases the interval might have been found to be shorter if more frequent tracings had been taken.

The six attacks of acute myocardial infarction described in the present series of cases, as well as in the series of Miller and Drori,[21] were preceded by periods of varying duration in which the patient suffered from angina pectoris. Delineation of the period of actual myocardial infarction from that of pure angina pectoris would be ill-defined and arbitrary. It would be difficult then to decide whether the T-wave changes described belong properly with the period of angina pectoris or with that of myocardial infarction. In four of these six episodes of acute infarction the phase of T-wave inversion was associated with such evidences of tissue breakdown as fever, leukocytosis or elevation of the sedimentation rate.

There is a large, well-founded body of opinion which separates from angina pectoris and acute myocardial infarction an intermediary type of response on the part of the heart to oxygen deprivation, namely, the status or phase of "coronary failure"[21-23] or "coronary insufficiency."[24-27] It might properly be maintained that the present T-wave changes are electrocardiographic manifestations, not necessarily the only type of electrocardiographic response, of that status. One could consider the subsequent electrocardiographic changes as the result of infarction of previously ischemic areas, whether or not these areas were then the site of small-scale necroses. In our opinion this is possible but unproved. The only fatal and autopsied case in this series, one of the two which never developed QRS changes, showed grossly evident infarction of a peculiar topographical distribution, namely an intramural infarct, which failed to involve the epicardium or endocardium. It would appear to be desirable to report, as much more convincing than any of the above-described cases, any instance of sequential changes, first in the T wave, then in the RS-T segment and QRS complex, occurring in a single, brisk, clear-cut episode of acute myocardial infarction not preceded by angina pectoris. To the best of our knowledge, such a case has not been described. The early T-wave changes as recorded in the experimental animal also deserve confirmation.

Inversion of the T waves is a nonspecific affair.[29] Among its many possible causes is myocardial ischemia. Although coronary insufficiency induced by various "stress tests" is generally manifested by a depression of the RS-T segments, a reversal in the direction of the T wave at the apical lead may similarly constitute a "positive" or "abnormal" test. Furthermore, areas of T-wave negativity, limited, as in the present cases, to or about lead V_4, have also been reported in apparently healthy males.[16] It is obvious from the present study that such changes, recorded in clinically suspect circumstances, may represent a dynamic development rather than a static condition and therefore demand careful continued study for the subsequent evolution of diagnostic electrocardiographic evidence of myocardial infarction.

The "transitional zone" of the QRS complex is currently regarded as that region at one side of which one type of QRS complex is recorded and at the other side of which another type of QRS complex is recorded. Depending upon

whether this zone lies parallel to the line of the usual six precordial leads, or intercepts the line of these leads more or less perpendicularly, the "transitional zone" may appear to be broad and distributed over two or more precordial positions, or it may be abrupt and closely demarcated. Depending upon the spatial orientation of the heart, this zone may be projected to one or more of the unipolar limb leads. Although there are some objections to the validity of this entire concept, in general the "transitional zone" is regarded as the projection upon the body surface of the plane of the interventricular septum. Since this plane must continue through the entire body, it must intercept the body surface twice. There must, therefore, be two such "transitional zones," one in a general way about 180 degrees around the torso from the other. Grant[30] has suggested that, just as there may be a "transitional zone" for the QRS complex, so may there be such a "transitional zone" for the T wave. If this is accepted, can one explain the areas of localized T-wave negativity described in the present series of cases as the result merely of the projection of two such transitional zones to an area within the confines of the usual six precordial leads, leads showing T-wave negativity being flanked by leads showing T-wave positivity? It seems difficult to imagine that the two extremities of this zone should lie so close to one another as the distance, say, from lead V_2 to lead V_5. This might assume that 180 degrees, more or less, of the circumference of the heart can be encompassed by moving the electrode 20 degrees or so on the precordium. This would seem to require a very small heart lying very close to the chest wall, or a very large chest wall closely opposed to a relatively normal sized heart. These postulates seem unlikely.

If, on the other hand, the plane of the "transitional zone" lies almost parallel with the line of the precordial leads, and since these six leads do not lie in a single straight line (leads V_3 and V_4 or V_4 and V_5 being staggered off that line), one can, as suggested by Grant,[30] postulate that the middle two or three precordial leads lie on the negative side of the "transitional zone" for T waves, while the flanking leads lie on its positive side. This explanation is entirely reasonable. However, as observed in the present study, the attendant and subsequent clinical course and their association when recorded with other electrocardiographic evidence of myocardial ischemia (e.g., positive Master test or postextrasystolic T-wave changes) make it much more likely, it seems to us, that these changes are to be regarded, somehow, as manifestations of myocardial ischemia.

Some of the earlier studies in which only a single apical lead showed T-wave inversion cannot be considered adequate for the present study. On more thorough exploration of the right side of the precordium this change might have been found to be associated, at that time, with definitive evidence of acute anteroseptal infarction. In such circumstances the inverted T waves would have represented "ischemia" at the margins of the infarct. Lepeschkin[31] has differentiated two types of pointed T-wave inversion in myocardial infarction, an early "ischemic" pattern associated with normal or shortened Q-T interval, and a later "post-ischemic" pattern associated with a prolonged Q-T interval. In the present study the Q-T interval was normal in cases 1, 4, 5, 6 and 7, prolonged in case 2 and shortened in case 3 at the phase of early T-wave inversion. When definitive electrocardiographic evidence of infarction was present, the Q-T interval was normal in cases 1, 4 and 5 and prolonged in cases 2, 3 and 6.

This discussion has been restricted to changes in certain of the precordial leads and their relation to subsequent anterior wall infarction. This is a reflection, we feel, of the anatomic fact that in the precordial leads alone is it possible in a general way to delineate the changes generated in a restricted area. This assumes the validity of the proposition that, although each of the leads in current use records the totality of the electrical changes produced in the heart as a whole, the individual leads, depending upon their proximity to the heart, are influenced to a much greater extent by changes in neighboring than in distant parts of the heart. Thus because of the relative remoteness of the left leg from the posteroinferior aspect of the heart, leads aV_F, II and III record the

total and composite effect of changes in the back of the heart. Likewise, depending upon the position of the heart, lead aV_L may reflect predominantly the changes produced in the entire lateral aspect of the heart. Were we able to record changes in selective portions of the posterior or lateral aspects of the heart, as we can on the anterior surface of the heart, it should be possible to demonstrate localized T-wave inversion in incipient myocardial infarction in the corresponding regions.

Conclusions

Inversion of the T waves, restricted to, or predominant in, circumscribed areas of the precordium, may precede, herald, or, at times, constitute an integral part of the electrocardiographic sequence of acute infarction of the anterior wall of the heart. These changes may remain fixed for long periods of time or show an instability in the direction toward or away from normality. In either case they may represent the clinical counterpart of an "ischemic" phase of myocardial infarction described in the experimental animal. The Q-T interval is generally normal when these changes are recorded but it may be shortened or lengthened. This experience emphasizes the need for protracted observation of patients showing these changes and justifies scepticism toward regarding them, especially under clinically suspect circumstances, as normal variations.

Sumario Español

La inversión de las ondas T, restringida a, o predominantemente en áreas circunscritas del precordio, puede preceder, anunciar, o, a veces, constituir una parte integral de la secuencia electrocardiográficia de infarto agudo de la pared anterior del corazón. Estos cambios pueden permanecer fijos por largos períodos de tiempo o mostrar una instabilidad en la dirección hacia lo normal o anormal. En uno u el otro caso puede representar la contraparte de la fase isquémica del infarto del miocardio descrito en el animal experimental. El intervalo Q-T es generalmente normal cuando estos cambios son registrados pero puede estar prolongado o acortado. Esta experiencia enfatiza la necesidad para una observación prolongada de pacientes que muestren estos cambios y justifica escepticismo en considerar estos cambios, especialmente bajo circunstancias de sospecha clínica como variaciones normales.

References

[1] Bayley, R. H., LaDue, J. S., and York, D. J.: Electrocardiographic changes (local ventricular ischemia and injury) produced in the dog by a temporary occlusion of a coronary artery, showing a new stage in the evolution of myocardial infarction. Am. Heart J. **27:** 164, 1944.

[2] —, —, and —: Further observations on the ischemia-injury pattern produced in the dog by temporary occlusion of a coronary artery. Incomplete T inversion, theophylline T reversion, and theophylline conversion of the negative T pattern. Am. Heart J. **27:** 657, 1944.

[3] —, and —: Electrocardiographic changes of impending infarction, and the ischemia-injury pattern produced in the dog by total and subtotal occlusion of a coronary artery. Am. Heart J. **28:** 54, 1944.

[4] Sampson, J. J., and Eliaser, M.: The diagnosis of impending acute coronary artery occlusion. Am. Heart J. **13:** 675, 1937.

[5] Waitzkin, L.: Impending myocardial infarction. Ann. Int. Med. **21:** 421, 1944.

[6] Feil, H.: Preliminary pain in coronary thrombosis. Am. J. M. Sc. **193:** 42, 1937.

[7] Boyer, N. H.: Premonitory symptoms of myocardial infarction. New England J. Med. **227:** 628, 1942.

[8] Jaffe, H. L., Halprin, H., and Nelson, L. M.: Evaluation of anginal pain in the various stages of coronary artery disease. Particularly the premonitory phase of coronary occlusion and infarction without occlusion. New York State J. Med. **47:** 1383, 1947.

[9] Dressler, W.: Myocardial infarction indicated by angina pectoris of effort or by brief attacks of angina of rest with remarks on premonitory pain. Am. Heart J. **28:** 81, 1944.

[10] Jaffe, H. L.: Electrocardiographic changes of coronary insufficiency during the formative stage of coronary occlusion. With a note on posterior location of anginal pain. J. Mt. Sinai Hosp. **16:** 404, 1949–50.

[11] Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., and Wilcox, B. B.: Coronary artery disease in man eighteen to thirty-nine years of age. Report of 866 cases, 450 with necropsy examinations. Am. Heart J. **36,** 334, 481 and 683, 1948.

[12] Littman, D., and Barr, J. H., Jr.: Acute atypical coronary artery insufficiency. Incidence and clinical course. Circulation **5:** 189, 1952.

[13] Freundlich, J.: Zur diagnostischen Bedeutung

der Brustwandableitungen. Acta. med. scandinav. **98:** 83, 1938–39.

[14] Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossman, C. E., Hecht, H., Cotrim, N., Meneses de Oliveira, R., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[15] Rosenbaum, F. F.: Clinical Electrocardiography. New York, Oxford University Press, 1950. P. 370 (52–91).

[16] Grant, R. P., Estes, E. H., Jr., and Doyle, J. T.: Spatial vector electrocardiography. The clinical characteristics of S-T and T vectors. Circulation **3:** 182, 1951.

[17] —: The relationship of unipolar chest leads to the electrical field of the heart. Circulation **1:** 878, 1950.

[18] Levine, H. D., Lown, B., and Streeper, R. B.: The clinical significance of postextrasystolic T-wave changes. Circulation **6:** 538, 1952.

[19] Graham, G. K., and Laforet, E. S.: An electrographic and morphologic study of changes following ligation of the left coronary artery in human beings. Am. Heart J. **43:** 1, 1952.

[20] Roesler, H., and Dressler, W.: Transient electrocardiographic changes identical with those of acute myocardial infarction accompanying attacks of angina pectoris. Am. Heart J. **47:** 520, 1954.

[21] Miller, D. C., and Drori, J. B.: "Ischemic" T waves as the earliest electrocardiographic change in myocardial infarction. New England J. Med. In press.

[22] Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathological findings. Am. Heart J. **19:** 1, 1940.

[23] —, —, and Zoll, P. M.: Angina pectoris, coronary failure and acute myocardial infarction. J.A.M.A. **116:** 91, 1941.

[24] Freedberg, A. S., Blumgart, H. L., Zoll, P. M., and Schlesinger, M. J.: Coronary failure: the clinical syndrome of cardiac pain intermediate between angina pectoris and myocardial infarction. J.A.M.A. **138:** 107, 1948.

[25] Master, A. M., Beebner, R., Dack, S., and Jaffe, H. L.: Differentiation of acute coronary insufficiency with myocardial infarction from coronary occlusion. Arch. Int. Med. **67:** 67, 1941.

[26] —, Jaffe, H. L., Dack, S., and Grishman, A.: Coronary occlusion, coronary insufficiency and angina pectoris. Am. Heart J. **27:** 803, 1944.

[27] —: Acute coronary diseases. Am. J. Med. **2:** 501, 1947.

[28] —, Dack, S., Grishman, A., Field, L. E., and Horn, H.: Acute coronary insufficiency: an entity. J. Mt. Sinai Hosp. **14:** 8, 1947.

[29] Levine, H. D.: The non-specificity of the electrocardiogram associated with coronary artery disease. Am. J. Med. **15:** 344, 1953.

[30] Grant, R. P. and Estes, E. H., Jr.: Spatial vector electrocardiography. Philadelphia, New York, Blakiston, 1951.

[31] Lepeschkin, E.: Modern Electrocardiography. Baltimore, Williams & Wilkins, 1951. Pp. 420–421.

The Misinterpretation of Electrocardiograms with Postprandial T-Wave Inversion

By Isidore Rochlin, M.D. and W. L. Jack Edwards, M.D.

Postprandial changes in the electrocardiogram are generally considered to be slight and not subject to misinterpretation. Four patients are presented in whom a diagnosis of coronary artery disease had been made because of flattening or inversion of the T waves in the bipolar or lateral V leads. The changes in T waves were temporary and could be produced by a high-carbohydrate meal. In addition, T-wave changes after a similar meal were studied in 85 normal young adults and 47 patients.

Observations on Original Patients

In four patients, two of them physicians, a diagnosis of coronary artery disease had been made, largely on the basis of occasional flattening or inversion of T waves in the bipolar or lateral V leads (V_4, V_5 and V_6). Coexisting chest pain, supposedly anginal, was present in two of these patients, and it was shown to be of noncardiac origin. It was found that the changes in the electrocardiogram could be induced at will by a high-carbohydrate meal and prevented by simultaneous administration of potassium chloride with the meal. Exercise did not lower the T waves in the same leads.

Changes in the electrocardiogram following meals have been described previously.[1, 2] These are generally considered to be slight and not subject to misinterpretation. It is known that changes following 100 Gm. of oral glucose are similar.[3] However, it is not generally appreciated that inversion of the T wave in any V lead or in leads II and III may be physiologic. For this reason, it was decided to report these patients.

Case Summaries

Patient A. S. This 42 year old business executive sought medical examination because of heavy business and civic responsibilities during the preceding year. His only symptom was shortness of breath, which proved to be sighing respiration when emotionally disturbed. At age 17 he had had an attack of acute rheumatic fever. However, he subsequently developed no cardiovascular symptoms and had passed many examinations for life insurance, always being told that his blood pressure was normal. His weight had been stable at 220 pounds for many years.

Physical examination revealed a robust, slightly overweight male. The resting blood pressure was 155/90. Examination of the heart revealed no enlargement, a regular rhythm, the second aortic sound equal to the second pulmonic sound, and a grade 1, soft, blowing, pulmonic systolic murmur.

Cardiac fluoroscopy was normal. The initial electrocardiogram showed low to flat T waves in leads I, II, aV_L, aV_F, V_5 and V_6. Extremely vigorous exercise for three minutes produced no significant change in the record and did not induce chest pain. Within 40 minutes after taking 100 Gm. of glucose while fasting, the T waves in leads II, III and V_6 became negative and slightly coved (fig. 1).

Patient R. P. This 34 year old physician was concerned about chest pain accompanied by electrocardiographic changes which had previously been interpreted as indicating coronary artery disease. Three years ago he began to have intermittent attacks of a sense of constriction and tightness around the costal margins with associated anorexia and nausea. These were not severe, sometimes lasted an entire day, and were not influenced by exertion. They were more frequent when he was emotionally upset, and usually came on several hours after a meal. The serum amylase was not elevated during these episodes. An oral cholecystogram revealed normal gallbladder function. An upper gastrointestinal series showed evidence of duodenitis and regurgitation of barium into the common bile duct. About two years previously he suddenly had a severe, stabbing pain over the precordium while driving an automobile. The pain persisted for 10 minutes and was accompanied by weakness and perspiration. He was admitted to a hospital where

From the Department of Medicine, Medical College of Alabama, Birmingham, Ala. Aided by a grant from the Life Insurance Medical Research Fund.

Dr. Edwards is a National Heart Trainee, National Heart Institute, National Institute of Health, U. S. Public Health Service.

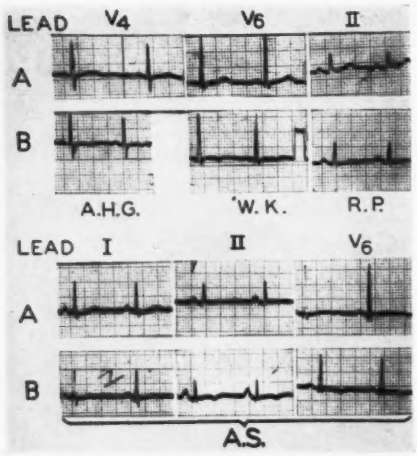


FIG. 1. Changes in T waves of four patients. *A* = fasting; *B* = 45 minutes after carbohydrate. Note T-wave inversion after oral carbohydrate in leads II (A.S.), V_4 (A.H.G.), and V_6 (W.K. and A.S.). Flattening of the T wave occurred in leads I (A.S.) and II (R.P.).

a diagnosis of suspected myocardial infarction was made on the basis of T-wave changes, although no fever, leukocytosis or increase in sedimentation rate occurred. After discharge he continued to have tightness around the costal margins, as well as vague aching sensations beneath the precordium and left scapula. Past history revealed the presence of labile hypertension, maximal 180/100, since age 19. In 1948, he had a brief episode of paroxysmal auricular fibrillation, followed by occasional premature beats.

On physical examination the patient appeared healthy. The blood pressure was 150/88. The heart was not enlarged. There was a grade 1 pulmonic systolic murmur which was considered physiologic.

Cardiac fluoroscopy revealed no abnormalities. The resting electrocardiogram was within normal limits. Strenuous exercise produced no pain in the chest or abdomen and did not significantly alter the electrocardiogram. On three separate occasions following a high-carbohydrate meal, the T waves became markedly flattened in leads I, II, aV_L, V_5 and V_6 (fig. 1). The administration of intravenous insulin produced a similar effect. These changes were identical with those which had previously been interpreted as indicating coronary arteriosclerosis. They did not occur when 3 Gm. of potassium chloride were taken with the high-carbohydrate meal.

Patient A. H. G. This 46 year old physician complained of chest pain, faintness and premature beats of three years duration. He actually had three varieties of pain, none of which was related to exertion or relieved by nitroglycerin. One was a bilateral, parasternal ache with tenderness on pressure, lasting 30 minutes or longer. A second ache was felt in the medial aspect of the left upper arm, extending down into the forearm, involving areas supplied by the radial and ulnar nerves. It recurred at short intervals, lasted only two or three minutes, and was associated only with motion of the left arm. The third pain was periapical and was felt coincidentally with extrasystoles, after which occurred a fleeting feeling of faintness and weakness lasting several minutes. Numerous previous electrocardiograms had shown variations in T waves from completely normal to flattened or inverted waves in several leads. Eating had appeared at times to cause lowering of the T waves and at other times to cause increased voltage.

Physical examination revealed a tender area in the left anterior chest wall. Pressure over this area reproduced his parasternal pain. There were no other positive findings. Films of the cervical and dorsal spine showed moderate osteoarthritis. Extremely vigorous exercise produced no chest pain or significant electrocardiographic change.

Forty-five minutes after a high-carbohydrate meal maximal T-wave inversion of 1.5 mm. occurred in lead V_4, with a return to the previous height of 1 mm. upright in 45 more minutes (fig. 1). This change was not observed after high protein meals with or without added potassium. There was no significant electrocardiographic effect of changes in position or respiration. Hyperventilation produced slightly lowered T waves in all leads without inversion.

Patient W. T. K. This 39 year old businessman was referred because of five attacks of chest pain and fainting, occurring between 1950 and 1952. Two attacks occurred just prior to supper, two just prior to breakfast, and one in the midmorning. All of the attacks occurred when the patient was either hurried or emotionally upset, and four occurred either during or within 30 minutes following severe exertion. Each attack began with weakness and dizziness, slight trembling of the hands, and deep breathing, followed by a rather severe pressing pain in the left parasternal area with radiation into the left shoulder and arm. Nitroglycerin had failed to relieve the chest pain; he had been given either a sedative or an opiate following each attack. Following the first attack he was admitted to the hospital, where an electrocardiogram revealed notched T waves in V_3 and an isoelectric T in lead III, without subsequent change. Thirteen years before, he had an episode of chills, fever and weight loss, which subsided spontaneously, only to occur again one year later. Between the episodes of fever, he developed a bullous eruption around the eyes and lower part of the face following a sunburn. A diagnosis of discoid lupus erythematosus was made. A mild anemia was also found at that time, which responded to iron therapy and has not recurred. The

skin lesions have been treated with bismuth, gold salts and Atabrine, the latter two having maintained a satisfactory remission during the past year.

Physical examination revealed a robust male with the yellow skin discoloration characteristic of Atabrine. The blood pressure was 120/70. Slight redness and scaling were noted over the butterfly area of the face. The heart was not enlarged and there were no murmurs.

The initial electrocardiograms revealed T waves of low amplitude in all leads. Extremely vigorous exercise terminated by weakness in the legs and dizziness produced no chest pain and did not significantly alter the electrocardiogram. Following 100 Gm. of sucrose orally, the T waves began to decrease in amplitude within 15 minutes, and within 45 minutes, the T wave was inverted in leads I, V_5 and V_6 (fig. 1). The patient was then given 6 Gm. of potassium chloride orally, and one hour later, the tracing appeared similar to the control. A second oral dose of sucrose and potassium together was not followed by any change. Hypoglycemia produced by insulin changed the electrocardiogram in the same fashion as did oral sucrose. The electrocardiographic effects of change in position, respiration and distention of both the stomach and colon with air were minimal.

Comment

Two patients had borderline hypertension which may have been responsible for the initially low T waves. Three showed inversion of T waves in lateral V leads after high-carbohydrate meals, and this could be prevented by potassium chloride (fig. 1). Insulin had the same effect as carbohydrate (table 1). It is of interest that exercise did not lower the T waves in these patients.

The ease with which these electrocardiograms may be interpreted as indicating coronary artery disease is quite evident. The group was too small for conclusions to be drawn concerning changes in vectors.

Studies on plasma potassium were done in one case (R.P.). His level fell from 4.1 to 3.6 mEq. per liter two hours after a high-carbohydrate meal. His plasma potassium dropped from 3.9 to 3.6 mEq. per liter even after the addition of 3 Gm. of potassium chloride to the meal. In the latter case, there were no changes in the electrocardiogram.

Observations on Control Subjects

To obtain more information concerning the frequency and mechanism of T-wave changes after high-carbohydrate intake, 85 normal adults and 47 patients (nine with arteriosclerotic heart disease) were studied. Frontal and spatial vector angles were measured, as were ventricular gradients. In a few cases, plasma potassium and glucose levels were determined.

Procedure

After a fast of at least four hours' duration, a control electrocardiogram was taken with the patient in the recumbent position. The positions of the V leads were indicated on the skin with a grease pencil, so that the same positions were used before and after the test. The subject then swallowed 100 Gm. of glucose dissolved in a glass of tap water. A second electrocardiogram was taken 45 minutes later. The subject remained in the recumbent position for three minutes before either tracing was recorded. A Sanborn Cardiette was employed.

Plasma Potassium and Glucose Determination. Venous blood was drawn into a heparinized syringe and then transferred to a centrifuge tube. After centrifugation, the supernatant plasma was drawn off and refrigerated. A Somogyi filtrate was prepared the same day. The glucose was determined in duplicate by the standard ferricyanide titration procedure of Hagedorn and Jensen.[4] For the determination of potassium, a 1:11 dilution of plasma with distilled water was prepared in duplicate. The concentration was measured with a Beckman flame photometer, using acetylene and oxygen. The working standards were distilled water solutions of potassium chloride which also contained sodium chloride (13 mEq. per liter).

Measurement of Vectors. The triaxial reference system was employed. Maximal deflections in any two of leads I, II and III were used to obtain frontal QRS and T vectors. Areas are better indicators of vector magnitudes than are deflections. However, the method was thought to be sufficiently accurate for our purposes. We were not concerned with the accuracy of the initial vectors, but rather with detecting the change after glucose.

Ventricular gradients were obtained by measuring the resultant of the QRS and T vectors in the frontal triaxial system.

The twin-cylinder apparatus described by Urschel and Abbey was used for visualization and measurement of the spatial vector angles.[5] The method was modified. It was observed that once the frontal vectors were set up, it was possible for the observer to tilt the apparatus so that only the disk edges were seen, while the disk surfaces were out of sight. With the aid of a protractor, the angle formed by the disks was then measured.

It is realized that the cylinder is not equally appropriate for all chests. Furthermore, in many

TABLE 1.—*Electrocardiographic Changes after Several Varieties of Clinical Procedures in Each Patient. (Note that after exercise the T waves remained the same or became slightly more upright, whereas oral intake of carbohydrate lowered or inverted the T waves. Frontal and spatial vector angle changes were inconstant. Ventricular gradient decreased in the three instances in which it could be measured)*

Patients	Procedures	Results
A.S.	1. 100 Gm. glucose	1. T isoelectric or low in I, II, aV_L, V_5 and V_6
B. P. 155/90 mm. Hg		Other changes:
		Frontal vector angle +67°
		Spatial vector angle +75°
		Ventricular gradient −31%
	2. 3 Gm. KCl	2. No change
	3. Severe exercise	3. T waves more upright
R.P.	1. High-carbohydrate meal	1. T flat in leads I, II, V_5 and V_6
B. P. 150/88 mm. Hg		Other changes:
		Frontal vector angle +39°
		Spatial vector angle −10°
		Ventricular gradient −3%
	2. Insulin	2. Same effect
	3. High-carbohydrate meal plus 3 Gm. KCl	3. No change
	4. Severe exercise	4. T waves remained upright
A.H.G.	1. High-carbohydrate meal	1. T inverted in lead V_4
B. P. 135/72 mm. Hg		Other changes:
		Frontal vector angle −17°
		Spatial vector angle −30°
		Ventricular gradient Not measurable
	2. Severe exercise	2. T waves remained upright
	3. High protein meal	3. No change
W.T.K.	1. 100 Gm. sucrose	1. T inverted in leads I, V_5 and V_6
B. P. 120/70 mm. Hg		Other changes:
		Frontal vector angle +20°
		Spatial vector angle +15°
		Ventricular gradient −9%
	2. Sucrose plus 3 Gm. KCl	2. No change
	3. Insulin	3. T inverted in leads I, V_5 and V_6
	4. Severe exercise	4. T waves more upright in leads I and V leads

cases no isoelectric or inverted T waves occurred in the V leads. The position of the transition zone was then estimated from the relative heights of the T waves in V_1 and V_6. This procedure may cause considerable error in the original positioning of the T disk. Again, there was much less error in measuring the change in the position of this disk.

Results in Healthy Young Adults

Changes in the Electrocardiogram. No change or a very slight change occurred in 30 of the 85 subjects. In the others, the following changes were observed: (1) T-wave depression occurred in leads II and III and in the V leads. Inversion of T waves was noted in one case in which spatial vector angles increased on only two of four tests. (2) U waves appeared or increased. (3) Premature contractions appeared or increased in three subjects, none of whom displayed significant changes in vectors.

Changes in Frontal Vector Angles. Nineteen subjects showed a change of their frontal vector angle greater than 15 degrees. A change of 15 degrees or less is within the error of the method. Of these 19, four had an increase in spatial vector angle of more than 20 degrees. There was no consistent trend.

TABLE 2.—*Changes in Normal Subject F. N., after Carbohydrate Intake with and without Added Potassium. (Note that added potassium either prevented or minimized the T-wave inversion in the precordial leads. Changes in ventricular gradient, frontal vector angles, spatial vector angle, and serum potassium were not constant when oral carbohydrate alone produced T-wave inversion. The greatest postcarbohydrate drop in serum potassium occurred when added oral potassium was given)*

Test	Changes in				Potassium		Glucose	
	ECG	Ventricular Gradient	Frontal Vector Angle	Spatial Vector Angle	mEq. Per Liter		mg. Per Cent	
					Before	After	Before	After
100 Gm. of glucose	T inverted in V_5 Biphasic in V_6	−8%	−2°	0°	3.85	3.85	99	202
High-carbohydrate meal	T inverted in V_3–V_6	Not measurable	0°	+30°	4.45	4.55	104	150
Glucose and 3 Gm. KCl	T biphasic in V_4 and V_5	Not measurable	+6°	+9°	4.55	4.45	80	147
High carbohydrate meal and 3 gm. KCl	No change	0	0	0	4.75	4.30	78	150

Changes in Spatial Vector Angles. Seven subjects showed a change in spatial vector angle beyond 20 degrees. A change of 20 degrees or less is within the experimental error. It is interesting that of the six subjects showing an increase, one had auricular premature beats before and after the test; another had a history of paroxysmal auricular tachycardia and subsequently showed ventricular premature beats before and after glucose. Glucose never produced paroxysmal auricular tachycardia in this individual.

Ventricular Gradients. Gradients could be measured in 62 subjects. There was no or slight change in 39. By slight change is meant an increase or decrease of less than 10 per cent. Eighteen showed an increase of more than 10 per cent, and five showed a decrease of more than 10 per cent.

The most interesting subject was F.N., who had a history of paroxysmal auricular tachycardia and who developed inversion of the T wave in multiple V leads.

The subject was a 29 year old white male who has had paroxysmal auricular tachycardia since 1951. He has had approximately 25 attacks characterized by sudden onset and less sudden cessation. Since February 1952, when he decided that anxiety brought them on, he has had only four attacks. These attacks were arrested by pressure on the carotid sinus or eye, or by the Valsalva maneuver. For the past year he has had ventricular premature beats, at the rate of about 10 per hour. On physical examination, he was found to be a short, stocky individual. His height was 64¾ inches. His weight was 163 pounds. His blood pressure was 130/70 in the left arm and 155/80 in the left leg. His pulse was regular with occasional premature beats. The heart rate was 72 per minute. The apex beat was felt in the fifth intercostal space in the midclavicular line. There were no abnormal sounds or murmurs. The femoral artery pulsations were palpable bilaterally. It was noted during fluoroscopic examination that the heart was unusually mobile during respiration. The aortic knob was not prominent.

T-wave inversion in his lateral V leads was discovered during routine testing. The glucose test was done three times and a high-carbohydrate meal was given once (table 2). On each occasion, inversion of the T waves in lateral V leads occurred (fig. 2). When the tests were repeated with added potassium chloride, only minute changes occurred. No inversion was observed. On four occasions, two with added potassium chloride, potassium and glucose levels were determined. Whereas most subjects show a slight decline in plasma potassium of about 0.2 mEq. per liter, his plasma potassium changed only once. This occurred when added potassium chloride was used but this did not prevent a decrease in plasma potassium.

The subject held his breath while V leads were recorded so that respiratory factors were ruled out. Changes in frontal vector angles were insignificant in all instances. Increases in spatial vector angles occurred only twice on four occasions. Ventricular gradients were not measurable, due to parallelism of the frontal vectors, except on one occasion, where a slight decrease occurred after glucose. No consistent change of any magnitude occurred in the various forces that were measured. Nevertheless, the oral glucose was consistently effective in pro-

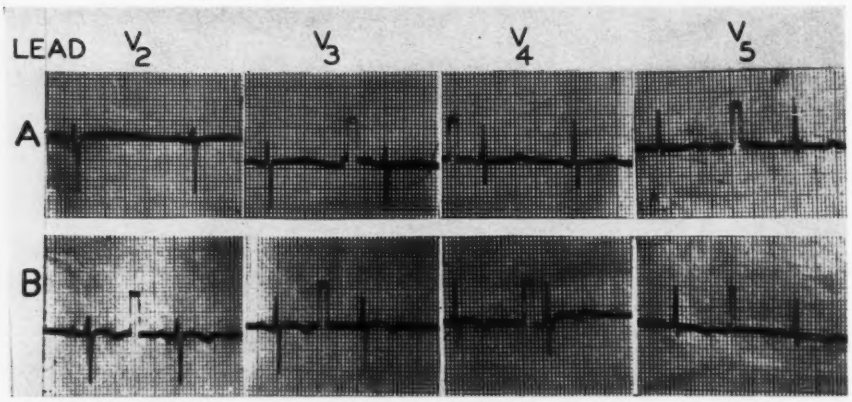


FIG. 2. Normal subject F. N. *A* = fasting; *B* = 45 minutes after 100 Gm. of glucose. Note marked T-wave inversion and slight coving of the RS-T segment in multiple precordial leads after oral carbohydrate. These changes did not occur when potassium chloride, 3 Gm., was ingested simultaneously with oral carbohydrate.

TABLE 3.—*Clinical Data Concerning the Nine Patients with Arteriosclerotic Heart Disease Given Oral Carbohydrate*

Patient	Sex	Age	Diagnosis
E.A.D.	M	70	Myo. Infarct.
C.D.E.	M	49	ASHD
H.G.	M	60	A. P.
P.L.	M	55	A. P.
L. M.	M	63	Myo. Infarct. and A. P.
R.P.	M	83	A. P.
H.R.	M	50	Old Myo. Infarct. and A. P.
C.D.S.	M	58	Old Myo. Infarct.
J.L.S.	M	51	Myo. Infarct. and A. P.

ASHD = Arteriosclerotic Heart Disease; Myo. Infarct. = Myocardial Infarction; A. P. = Angina Pectoris.

ducing marked changes in T waves, and these changes are subject to misinterpretation.

Patients with and without Heart Disease

Thirty-nine patients without heart disease and nine with arteriosclerotic heart disease were tested. Pertinent clinical date concerning the latter group are presented in table 3. Although infrequent inversion of the T wave did occur in lateral V leads (table 4), the number of subjects in each group is too small for accurate estimation of the incidence of this phenomenon. Changes in vector forces were inconsistent.

TABLE 4.—*Summary of Changes in Three Groups of Subjects. (T-wave lowering was no more frequent in patients with arteriosclerotic heart disease than in normal young healthy males. Vector angle and ventricular gradient changes were not constant.)*

	Normal Subjects	Patients without Heart Disease	Patients with Arteriosclerotic Heart Disease
Number Studied	85	38	9
ECG's:			
Diminished T-wave voltage in	55	9	5
T-wave inversion in V lead in	1	0	1
Premature contractions in	3	1	0
Frontal Vector Angles:			
Increased more than 15° in	13	6	1
Decreased more than 15° in	6	2	2
Spatial Vector Angles:			
Increased more than 20° in	6	4	1
Decreased more than 20° in	1	4	1
Ventricular Gradients:			
Measured in	62	16	16
Increased more than 10% in	18	3	1
Decreased more than 10% in	5	2	1

DISCUSSION

The Effect of Meals on the Electrocardiogram. It is known that after a meal there is a tendency for the T waves to become lower.[1, 2] This may be due to a sympathetic effect which decreases plasma potassium. Another explanation is that a decrease in plasma potassium is brought

about by the entrance of food into the gastrointestinal tract which stimulates the secretion of insulin. The insulin in turn stimulates the liver and skeletal muscle to deposit potassium with glycogen.[3] It is known that 100 Gm. of oral glucose lowers the plasma potassium in a similar fashion.[6]

The Effect of 100 Gm. of Oral Glucose on the Electrocardiogram. We were unable to find recent references to the effect of oral glucose on the electrocardiogram, with the exception of unpublished observations of Goldberger.[3] He reported flattening of the T waves in leads I and II and in the V leads; in addition, T-wave inversion was noted in lead III in a normal young female. As one might expect, the changes were more marked than those seen after ordinary meals which contained more potassium and less carbohydrate. As has already been mentioned, these changes are attributed to insulin and the accompanying hypopotassemia. It is well known that the effects of hypopotassemia are not closely correlated with the actual plasma levels.[7] The method of lowering the level must be taken into account. A redistribution of myocardial potassium produced by either a changing blood glucose level or by insulin, or both, has not been described in man.

Normal subjects and those with arteriosclerotic heart disease showed the same response to the test. Despite definite trends of T-wave lowering, no consistent changes were detected in spatial vector angles or in ventricular gradients. T-wave inversion in lateral V leads was produced by physiologic mechanisms in both normal and abnormal subjects. A high-carbohydrate meal had the same effect as 100 Gm. of oral glucose, and this effect could be prevented by the addition of 3 Gm. of potassium chloride to the meal.

Conclusions

1. High-carbohydrate meals can be responsible for flattening or inversion of the T wave in bipolar leads or in any V lead. This can be prevented by potassium chloride. Failure to recognize this fact has led to a mistaken diagnosis of coronary vessel disease in four patients, two of whom were physicians.

2. The mechanism may involve redistribution of intracellular myocardial potassium, following the liberation of insulin.

3. Associated changes in vectors and in ventricular gradients are not consistent.

Sumario Español

1. Comidas altas en hidratos de carbono pueden ser responsables del aplastamiento o inversión de las ondas T en derivaciones bipolares o en cualquier derivación V. Esto puede ser evitado por el cloruro de potasio. No tener en cuenta este factor ha conllevado al error diagnóstico de enfermedad coronaria en cuatro pacientes, dos de los cuales eran médicos.

2. El mecanismo puede envolver la redistribución del potasio intracelular del miocardio, como consecuencia de la liberación dd insulina.

3. Cambios asociados en vectores y en pendientes ventriculares no son consistentes.

REFERENCES

[1] Gardberg, M., and Olsen, F.: Electrocardiographic changes induced by the taking of food. Am. Heart J. **17:** 725, 1933.

[2] Simonson, E., Alexander, H., Henschel, A., and Keys, A.: The effect of meals on the electrocardiogram in normal subjects. Am. Heart J. **32:** 202, 1946.

[3] Goldberger, E.: Unipolar Lead Electrocardiography and Vectorcardiography, ed. 3. Philadelphia, Lea & Febiger, 1953. P. 161.

[4] Hagedorn, H. C., and Jensen, B. N.: Zur Mikrobestimmung der Blutzuckers Mittels Ferricyanid. Biochem. Ztschr. **135:** 46, 1923.

[5] Urschel, D. L., and Abbey, D. C.: Mean spatial vectorcardiography. The normal QRS and T vectors. Am. Heart J. **45:** 65, 1953.

[6] Aitkin, R. S., Alliott, E. N., Castleden, C. I. M., and Walker, M. B.: Observations in a case of familial periodic paralysis. Clin. Sc. **3:** 47, 1937.

[7] Currens, J. H., and Crawford, J. D.: The electrocardiogram and disturbance of potassium metabolism. New England J. Med. **243:** 843, 1950.

Repeat Variability of Spatial QRS and T Vectors

By Ernst Simonson, M.D., and Ancel Keys, Ph.D.

In spite of the increasing literature on spatial electrocardiographic vectors, no information on their repeat variability is available. Such data are presented in this paper and compared with the repeat variability of conventional electrocardiographic items, as background for interpretation of changes in direction and magnitude of spatial vectors in patients.

THE interindividual variability of spatial electrocardiographic vectors was recently studied in 178 older men and normal standards and correlations were given.[1] However, no information about repeat variability of spatial vectors has been available so far, although such information would be essential for interpretation of changes of spatial vectors in physiologic stress or in disease.

Method and Subjects

The mean spatial QRS and T vectors were constructed from the conventional Electrocardiogram by means of a recently developed method.[2] The values are expressed in H° = azimuth, V° = elevation, Mag = magnitude, and dA° = angle between spatial QRS and T vectors. In regard to H°, the reference line is a parallel to lead I passing through the hypothetic center of the heart from left (0°) to right ±180°, with an anterior positive and a negative posterior hemisphere. V° is the angle between the vector and a vertical projection through the center. Mag is in terms of standardized millimeters (1.0 mm. = 0.1 mv.) All precordial leads were taken at the fifth intercostal level, but otherwise similarly to the clinical routine procedure; no special effort was made to insure the absolute identity of the precordial electrode positions on repetition. In this respect, this series differs from an earlier investigation,[3] in which the electrode position was marked with intracutaneous dye injection. The variability is expressed in terms of repeat standard deviation SD_w, as compared with the standard deviation SD_i of the group. The variability of spatial vectors was compared with that of some electrocardiographic items in conventional leads.

From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

This investigation was supported by research grants H-10(C7) from the National Heart Institute, U. S. Public Health Service, and the Minnesota Heart Association.

Two groups were investigated: (a) 20 men between 20 and 30 years, with an interval of one week between repetitions, and (b) 50 men between 50 and 60 years, with an interval of one year between repetitions. A careful clinical and laboratory investigation, which included the response to various physiologic stresses, revealed no sign of any disease.

Results and Discussion

For the group of young men table 1 shows a comparison of the magnitude of the spatial QRS and T vectors with the sum of QRS and T amplitudes in leads I, II, III (Σ_{QRS}, Σ_T). These items were found to have a low repeat variability in our former study.[3] In contrast, the RS amplitude and T amplitude in V_4 were expected to show greater variability due to inadvertent variation of electrode location. Σ_{QRS} and Σ_T are free from this source of variability, but it enters into the measurement of QRS-Mag and T-Mag.

The group was tested in the interval of one week. Owing to the different magnitude of the means in these various items (row a), the absolute standard deviations are not directly comparable, but SD_w in per cent of the mean (row 5) is of the same order in QRS-Mag and Σ_{QRS}, while it is higher for T-Mag than for Σ_T, probably in part because of the variability in electrode position, as shown by the high variability of SD_w for V_4. Especially important is the comparison of inter-individual or group variability with the intraindividual or repeat variability, because their ratio shows the reliability of the method to characterize the position of a given individual within the group. The ratio of SD_w–SD_i is similar for QRS-Mag and Σ_{QRS}, while that of T-Mag is between Σ_T and T-V_4.

TABLE 1.—*Interindividual (SD_i) and Intraindividual (One Week) Variability (SD_w) in 20 Young Men. Comparison of the Magnitude of the Spatial QRS and T Vectors with Amplitudes in Conventional Leads*

	Spatial Vectors		Conventional Leads			
	QRS Mag.	T Mag.	Σ_{QRS}	Σ_T	RS-V_4	T-V_4
Mean (a)	11.7	3.90	28.0	6.18	27.5	6.92
SD_i (b)	3.12	1.22	6.83	1.93	6.41	2.73
Mean Δ	0.26	−0.18	0.38	−0.39	−0.92	−0.60
SD_w (c)	1.46	0.92	2.76	0.86	5.69	2.36
c/a × 100	12.5	23.6	9.9	13.9	21.4	34.1
c/b × 100	46.7	75.2	40.4	44.6	88.9	86.5

TABLE 2.—*Interindividual (SD_i) and Intraindividual (One Week) Variability (SD_w) in 20 Young men. Comparison of the Direction of the Spatial QRS and T Vectors (H° = Azimuth, V° = elevation, dA° = Angle between Spatial QRS and T Vectors) with the Einthoven QRS and T Axes*

	Spatial Vectors					Axes	
	QRS		T		dA°		
	H°	V°	H°	V°		QRS°	T°
Mean (a)	−25.5	38.8	34.8	66.8	57.0	55.9	28.0
SD_i (b)	21.6	21.8	12.1	20.2	19.6	25.0	23.3
Mean Δ	−4.8	2.5	−0.95	2.4	3.6	−1.6	−3.1
SD_w (c)	19.1	9.5	10.9	14.4	14.6	9.2	15.7
c/b × 100	88.5	43.5	90.5	71.3	74.6	36.8	67.5

Table 2 shows a comparison of the direction of spatial vectors with the Einthoven QRS and T axes. The SD_w of QRS-V° and T-V° are very similar to the SD_w of the QRS and T axes. This is understandable, because the (frontal plane) Einthoven axes are primarily related to V°. The ratio of SD_w–SD_i is also in the same order of magnitude in these items. It is considerably higher in the other spatial angles, probably because of variation of the precordial electrode position, which is primarily related to H°.

Tables 3 and 4 show the corresponding values of the group of 50 older men who were studied twice, with an interval of one year between studies. So far as the comparison with the conventional electrocardiographic items is concerned, the results are quite similar to those of the younger group. The ratio SD_w–SD_i is nearly identical for QRS-Mag and Σ_{QRS}, but is higher for T-Mag than Σ_T. Further, the

TABLE 3.—*Interindividual (SD_i) and Intraindividual (One Year) Variability (SD_w) in 50 Older Men Comparison of the Magnitude of the Spatial QRS and T Vectors with Amplitudes in Conventional Leads*

	Spatial Vectors		Conventional Leads				
	QRS Mag.	T Mag.	Σ_{QRS}	Σ_T	R_2	T_2	T-V_4
Mean (a)	9.30	3.39	20.29	5.03	7.95	2.37	5.64
SD_i (b)	3.36	1.11	5.89	1.73	3.34	0.96	2.20
Mean Δ	0.24	−0.07	2.26	0.03	0.28	−0.01	1.41
SD_w (c)	1.87	1.06	3.17	1.14	1.48	0.49	1.66
c/a × 100	20.1	31.5	15.7	22.7	18.6	21.1	29.4
c/b × 100	55.6	95.5	54.5	65.9	44.7	51.1	75.5

TABLE 4.—*Interindividual (SD_i) and intraindividual (One Year) Variability (SD_w) in 50 Older Men. Comparison of the Direction of the Spatial QRS and T Vectors (H° = Azimuth, V° = Elevation, dA° = Angle between Spatial QRS and T Vectors) with the Einthoven QRS and T Axes*

	Spatial Vectors					Axes	
	QRS		T		dA°		
	H°	V°	H°	V°		QRS°	T°
Mean (a)	−24.9	52.1	46.1	61.3	59.0	40.9	39.0
SD_i (b)	19.94	27.72	15.34	15.68	21.74	28.9	18.9
Mean Δ	0.20	−0.15	−3.4	−4.9	−2.7	0.1	2.6
SD_w (c)	12.84	8.80	8.45	12.66	14.69	10.1	15.2
c/b × 100	64.4	31.7	55.0	80.7	67.5	35.0	80.5

SD_w for QRS-V° and T-V° is not significantly different from that of the QRS and T axes, respectively. For neither group is there evidence of superiority of spatial vectors, as compared with conventional electrocardiographic items, in the characterization of a given individual within the group.

Table 5 shows a comparison of the repeat variability of 20 young men within one week with that of the 50 older men within one year in conventional electrocardiographic items. The SD_w is of the same order of magnitude in both groups except for T-V_4, which is smaller in the older group (significant at the 5 per cent level).

Table 6 shows the corresponding comparison of spatial vectors. The SD_w for H° and V° is somewhat smaller for the older men, but the difference was statistically not significant. The SD_w of dA° is identical in both groups. The SD_w–SD_i ratios are somewhat smaller in the older men except for T-V°. On the other

TABLE 5.—*Conventional Leads. Comparison of Repeat Variability of 20 Young Men within One Week and of 50 Older Men within One Year*

	Σ_{QRS}	Σ_T	T-V_4	QRS axis	T axis
Young Men					
SD_i (b)	6.83	1.93	2.74	25.0	23.3
SD_w (e)	2.76	0.86	2.36	9.2	15.7
e/b × 100	40.4	44.6	86.5	36.8	67.5
Older Men					
SD_i (b)	5.89	1.73	2.20	28.9	18.9
SD_w (e)	3.17	1.14	1.66*	10.1	15.2
e/b × 100	54.5	65.9	75.5	35.0	80.5

* $p < 0.05$

TABLE 6.—*Spatial Vectors. Comparison of Repeat Variability of 20 Young Men within One Week and of 50 Older Men within One Year*

	QRS			T			dA°
	H°	V°	Mag.	H°	V°	Mag.	
Young Men							
SD_i (b)	21.6	21.8	3.12	12.1	20.2	1.22	19.6
SD_w (e)	19.1	9.5	1.46	10.9	14.4	0.92	14.6
e/b × 100	88.5	43.5	46.7	90.5	71.3	75.2	74.6
Older Men							
SD_i (b)	19.9	27.7	3.36	15.3	15.7	1.11	21.7
SD_w (e)	12.8	8.8	1.87	8.5	12.7	1.06	14.7
e/b × 100	64.4	31.7	55.6	55.0	80.7	95.5	67.5

hand, the SD_w and SD_w–SD_i ratios for QRS-Mag and T-Mag are somewhat smaller in the group of younger men, but these differences are not statistically significant.

The comparison of the two groups includes the factor of age as well as that of the time interval between the repeats. For technical reasons it was not possible to repeat the older group within one week and the younger group within one year, and therefore these factors cannot be separated. However, it is surprising that the repeat variability of the older group within one year is not larger than that of the younger group within one week.

TABLE 7—*Correlation Coefficients (r) for Repeat Variability of Spatial Vectors. Y = 20 Young Men, O = 50 Older Men, T = Total Group*

Correlation	Group		
	Y	O	T
QRS-H° vs. QRS-V°	−0.52*	−0.24*	−0.36†
T-H° vs. T-V°	0.31	0.05	0.18
QRS-Mag. vs. T-Mag.	0.18	0.39†	0.35†

* $p < 0.05$. † $p < 0.01$.

Table 7 shows the correlation between changes of QRS-H° versus V°, T-H° versus T-V°, and QRS-Mag versus T-Mag. While the interindividual variability of the azimuth (H°) and elevation (V°) is largely independent,[1] there is a highly significant negative correlation between the changes of QRS-H° and QRS-V° in the total group and the younger group. The correlation in the older group is close to the 5 per cent level of significance. This is also illustrated by figure 1. On the other hand, there is a significant positive correlation between T-H° and T-V° for the younger, but not for the older or total group. This means that the correlation between QRS-H° and QRS-V° cannot be due to a positional change, since this would affect both the QRS and T vector in the same way.

There was a highly significant positive correlation between QRS-Mag and T-Mag in the older and the total group. We found in an earlier study that the interindividual correlation between these items was also positive,[1] in disagreement with the concept of the ventricular gradient,[4] which implies a negative rather than positive correlation.

At that time, the reservation was made that the ventricular gradient concept might hold better for intraindividual variations, since several of the causes for the existence of a ventricular gradient are structural. The positive correlation between the intraindividual variations of QRS-Mag and T-Mag shows that the ventricular gradient concept is also not valid for intraindividual changes. It is true that this series is concerned with amplitudes and not with areas, but in normal electrocardio-

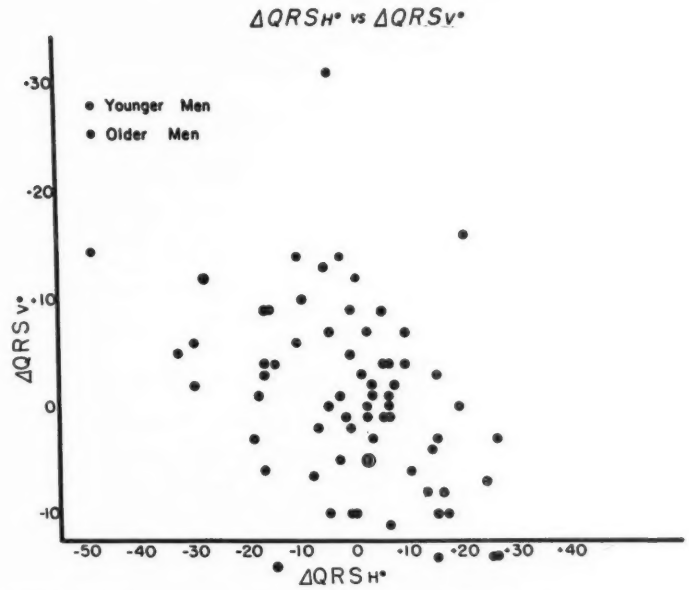


FIG. 1. Correlation between the changes of the azimuth (H°) and elevation (V°) of the mean spatial QRS vector.

grams the correlation between area and amplitude is so high that one can be predicted from the other.[4]

The high repeat variability of the spatial vectors is undoubtedly due, in large part, to variation in the position of the precordial electrodes. If spatial vector analysis is used for the follow-up of patients, a semipermanent marking of the points for the electrode positions is even more important than for conventional interpretation.

SUMMARY

1. The repeat variability of spatial QRS and T vectors was compared with the repeat variability of conventional electrocardiographic items in a group of 20 normal young men, with an interval of one week between the repeat studies, and in a group of 50 normal older men, with an interval of one year between the repeat studies.

2. The vectors were constructed from the conventional electrocardiogram and expressed in terms of azimuth (H°), elevation (V°), and magnitude; the angle between the spatial QRS and T vectors was also measured.

3. Repeat variability was expressed as intra-individual standard deviation (SD_w) and compared with the interindividual standard deviation (SD_i) and the mean of the group. No special precaution was made to insure identical precordial lead positions in the replications.

4. The repeat variability of spatial vectors was quite large in both groups. There was no superiority of spatial vectors in characterizing an individual within the group.

5. The variability of conventional electrocardiographic items as well as that of spatial vectors was not greater in the group of older men within one year than it was in the younger group within one week.

6. There was a highly significant negative correlation between the changes of H° and V° of the QRS vector, and some positive, but statistically not significant, correlation between the changes of H° and V° of the T vector.

7. There was a significant positive correlation between the changes of the magnitude of the QRS and T vectors, in disagreement with the concept of the ventricular gradient.

Sumario Español

1. La variabilidad repetida de los vectores QRS y T fué comparada con la variabilidad repetida de ítems convencionales electrocardiográficos en un grupo de 20 hombres jovenes, con un intervalo de una semana entre los estudios repetidos y en un grupo de 50 hombres mayores, con un intervalo de un año entre los estudios repetidos.

2. Los vectores fueron construidos del electrocardiograma convencional y expresados en términos de azimut (H°), elevacion (V°) y magnitud; el ángulo entre los vectores espaciales QRS y T fué también determinado.

3. La variabilidad repetida fué expresada como una desviación uniforme intraindividual (SD_w) y comparada con la desviación uniforme interindividual (SD_i) y el promedio del grupo. No se tomó precaución especial alguna para asegurar posiciones precordiales en las derivaciones réplicas.

4. La variabilidad repetida de vectores espaciales fué bastante grande en ambos grupos. No hubo superioridad en los vectores espaciales en caracterizar un individuo dentro de un grupo.

5. La variabilidad de ítems convencionales electrocardiográficos al igual que aquella de vectores espaciales no fué mayor en el grupo de hombres mayores durante un año que en el grupo de hombres jovenes durante una semana.

6. Hubo una correlación negativa significativa entre los cambios de H° y V° del vector QRS y algunas positivas, pero estadisticamente no significativas, correlaciones entre los cambios de H° y V° del vector de T.

7. Hubo una correlación positiva significativa entre los cambios de la magnitud de los vectores QRS y T, en desacuerdo con el concepto de la pendiente ventricular.

REFERENCES

[1] Simonson, E., and Keys, A.: The spatial QRS and T vector in 178 normal middle-aged men. Circulation **9:** 105, 1954.

[2] —: A spatial vector analyzer for the conventional electrocardiogram. Circulation **7:** 403, 1953.

[3] —, Brozek, J., and Keys, A.: Variability of the electrocardiogram in normal young men. Am. Heart J. **38:** 407, 1949.

[4] —, Schmitt, O. H., Dahl, J., Fry, D., and Bakken, E. E.: The theoretical and experimental bases of the frontal plane ventricular gradient and its spatial counterpart. Am. Heart J. **47:** 122, 1954.

Electrocardiographic Findings in Epidemic Hemorrhagic Fever

By CARL M. PEARSON, CAPT., MC, USAR, AND ROBERT J. HALL, MAJ., MC, USA

Mounting experiences with the newly discovered disease, epidemic hemorrhagic fever indicate that the basic pathologic lesion affects the vascular system. An electrocardiographic survey in 53 cases has disclosed that during the acute phase of the illness more than 50 per cent of patients show alterations. These, however, are nonspecific and resemble changes recorded in other acute infections. There was no clinical or electrocardiographic evidence of residual cardiac injury in many cases reevaluated up to six months after the acute illness.

DURING the late spring and fall seasons of 1952 the members of the medical service of the 11th Evacuation Hospital stationed in Korea cared for 53 cases of epidemic hemorrhagic fever. The patients were young men, and all but three were from the United States Armed Forces, one of the remainder was from the Turkish Brigade, and the other two from the Republic of Korea Army. The disease presented itself in all degrees of severity from a mild afebrile type, with minimal physical and laboratory findings, to an intensely severe form requiring prolonged hospitalization and convalescence. There were two deaths. All patients were seen in the acute stage of their illness and were followed throughout the disease. Many were evaluated at three- and six-month follow-up periods. The general nature of the disease has been presented in a recent symposium,[1] and the present cases were similar in symptomatology and course to those described therein. Recently, somewhat similar electrocardiographic alterations have been briefly recorded in other series.[2, 3]

Early in the course of evaluation of these patients, it was noted that a significant number showed evidence of electrocardiographic alteration, and hence all subsequent cases were followed with one or more electrocardiographic tracings which included standard limb leads, unipolar limb leads and chest V leads. The vector method of cardiographic analysis as outlined by Grant and Estes[3] and others was utilized when indicated. In all, 150 tracings were made on the 53 patients in the acute and convalescent phases, an average of nearly three per patient. Twenty-eight patients, or slightly more than one half, showed an abnormality in the electrocardiogram and 25 showed no abnormality. Most of the abnormalities were temporary and the tracings reverted to normal within several days.

There was no single diagnostic change observed, but in general the abnormalities were of four types: (1) T-wave alterations suggestive of a myocardial ischemia; (2) prolongation of the QRS complex indicative of a conduction defect; (3) T-wave peaking and Q-T prolongations suggesting electrolyte imbalances; and (4) bradycardia. No arrhythmias or A-V conduction defects were encountered. In some cases more than one of the above types of change were noted simultaneously or on consecutive tracings. S-T segment deviations were present in three cases. These suggested a focal anterior pericarditis.

The most common abnormality was that involving a shift in the direction of the T-wave vector. This change was seen in 14 patients. Invariably it was present early in the disease (third to fifth day) and was often correlated with a pronounced febrile state. Vascular hypotension and advanced uremia were not usually present at this time. The T waves were usually inverted in lead III, were inverted or diphasic in lead II, and, in two instances, were inverted in all three standard limb leads (fig. 1). The QRS-T spatial vector angle, normally 45 degrees or less, was widened in all 14 cases to between 85 and 180 degrees. These altera-

From the Medical Service, 11th Evacuation Hospital, Korea.

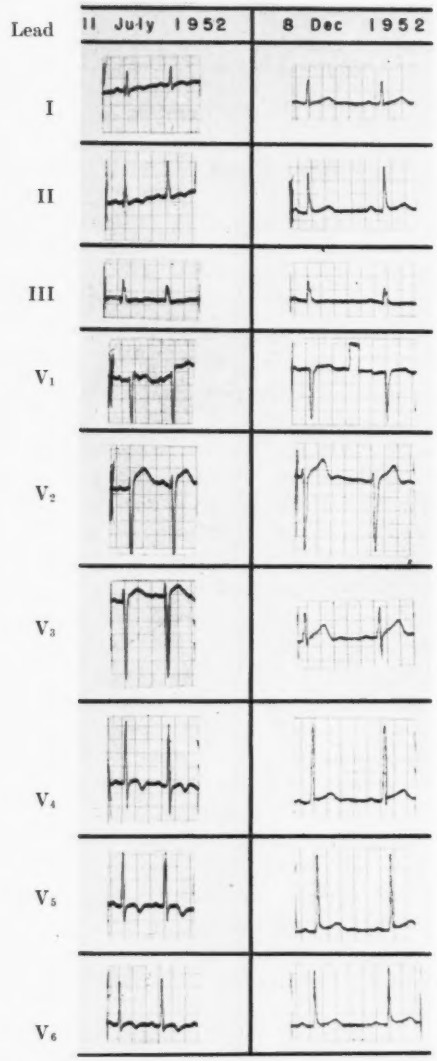


FIG. 1. T-wave alterations during the acute phase of hemorrhagic fever. Return to normal on follow-up tracing.

tions were characteristic of varying degrees of myocardial ischemia and strain. In all cases where serial tracings were available, the tracings reverted to normal in from 2 to 15 days. In conjunction with the above findings, or occurring separately, were low-voltage T waves in all leads on six occasions (fig. 2). These also reverted to normal within a few days. In one

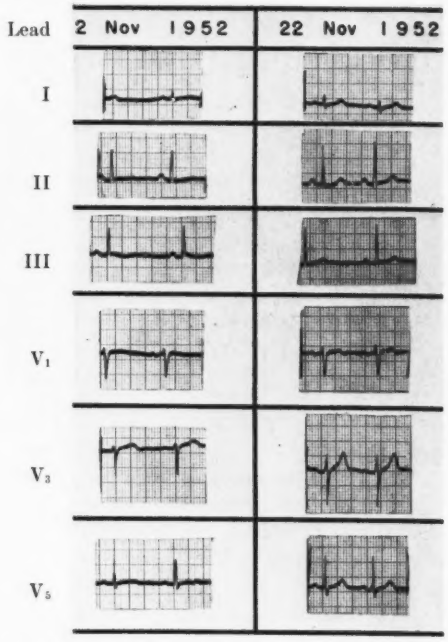


FIG. 2. Low voltage T-waves during acute illness. Return to normal three weeks later.

instance, in a patient with very severe necrotizing tracheobronchitis and pneumonitis, the pattern was typical of acute cor pulmonale. This patient ultimately recovered after coughing up large necrotic casts of his respiratory tree. The electrocardiogram also returned to normal.

Evidence of delayed intraventricular conduction time was present in five cases. The duration of the QRS ranged from 0.10 to 0.13 second, and the degree of block varied in several cases from time to time. Two were examples of right bundle-branch block (fig. 3), and the other three of an intermediate or indeterminate type. In four out of the five the block disappeared early, and in the fifth it was still present six months after the acute illness.

Tall peaked T waves were present six times. They were most prominent in the precordial leads and almost invariably coincided with the maximum period of anuria (fig. 4). They were characteristic of moderate degrees of hyperkalemia. The Q-T intervals were prolonged in three of the above cases, also at the height

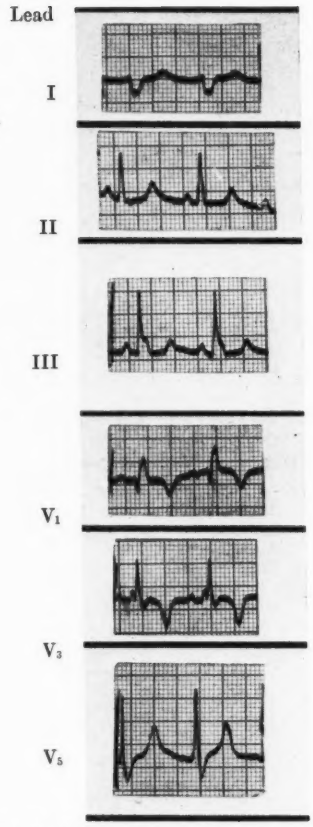


FIG. 3. Right bundle-branch block in acute phase of hemorrhagic fever. This patient subsequently died.

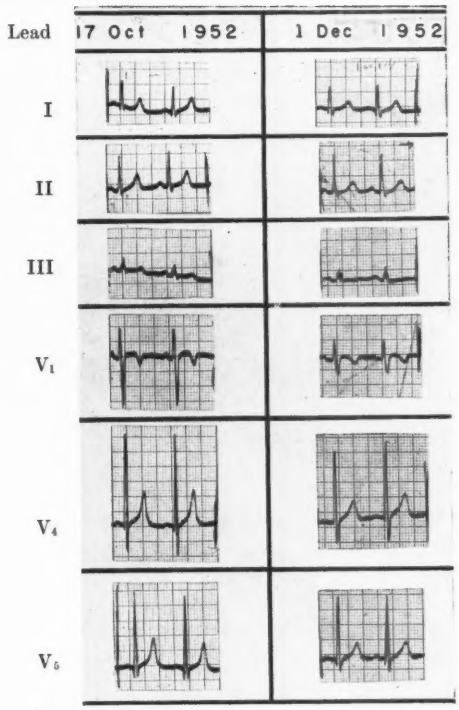


FIG. 4. T-wave peaking compatible with mild hyperpotassemia during the oliguric phase, contrasted with a tracing taken after recovery.

of uremia, suggesting some concomitant hypocalcemia. These changes were transient and disappeared as soon as adequate diuresis was established. No example of hypokalemia during the diuretic phase was encountered.

Bradycardia (rates below 60 per minute) was seen in 11 patients. It occurred early in the convalescent phase of the illness, was not associated with fever and usually developed during the diuretic period. In none of these was there an accompanying bundle-branch block. Rates as low as 40 or 45 per minute were not uncommon.

DISCUSSION

The occurrence of a significant number of electrocardiographic alterations in epidemic hemorrhagic fever is not surprising when one considers the pathologic anatomy of this disease. The basic defect is a widespread capillary damage[5] with its sequelae in multiple organs and systems. In this regard it resembles several of the rickettsial diseases. Specifically the heart has shown subepicardial and subendocardial hemorrhages, especially into the atria, and cellular infiltrates into areas in the myocardium, endocardium and epicardium.

The electrocardiographic changes, particularly the T wave alterations, are rather "nonspecific" and are known to occur in some other infectious diseases.[6] These include diphtheria, acute rheumatic fever, typhus and scrub typhus, infectious mononucleosis, poliomyelitis (early in the febrile stage), and others.

In the present cases the QRS and T-wave changes are most closely correlated with the maximum temperature and the crisis of the illness, and these alterations may represent

the effects of fever and its increased metabolic demands on the myocardial musculature. It is likely, too, that other factors come into play at this time. These include: (1) acute circulatory insufficiency due to hemoconcentration, peripheral circulatory collapse, and others; (2) sympathetic and vagal nerve action; (3) relative coronary insufficiency; and (4) toxic effects of the infectious agent on the heart.

It is important to record that despite the relatively high percentage of alterations noted early in the disease, no evidence of permanent cardiac damage has been observed in this series, with the possible exception of a persistent bundle-branch block, of no obvious clinical significance, in one case. It is entirely possible that the latter defect may have been present prior to the onset of the hemorrahagic fever in this case.

Summary

In a total of 53 cases of acute epidemic hemorrhagic fever serial electrocardiograms revealed a variety of alterations in 28, or 53 per cent.

In general the changes were of four types: (1) T-wave variations both in direction and amplitude; (2) bundle-branch block; (3) evidence of electrolyte imbalances; and (4) bradycardia.

With one possible exception there were no evidences of residual cardiac damage on tracings taken in many cases three and six months after the acute illness. Hence latent heart disease should not be of concern to persons who have suffered with this disease.

Sumario Español

En un total de 53 casos de fiebre hemorrágica epidémica aguda electrocardiogramas en serie revelaron una variedad de alteraciones en 28 o sea 53 por ciento.

En general los cambios fueron de cuatro tipos: (1) variaciones en la onda T en dirección y amplitud; (2) bloqueo de rama; (3) evidencia de desbalance electrolítico; y (4) bradicardia.

Con una posible excepción no hubo evidencias de daño residual cardíaco en los trazados obtenidos en muchos casos tres y seis meses luego de la enfermedad aguda. Por lo tanto aquellas personas que han sufrido esta enfermedad no deben de preocuparse en cuanto se refiere a enfermedad cardíaca como resultado de la misma.

REFERENCES

[1] A symposium on epidemic hemorrhagic fever. Ann. Int. Med. **38:** 53, 1953.

[2] Barbero, G. J., Katz, S., Kraus, H., and Leedham, C.: Clinical and laboratory study of 31 patients with hemorrhagic fever. Arch. Int. Med. **91:** 177, 1953.

[3] Watson, J. H.: Sequelas of epidemic hemorrhagic fever in the convalescent patient. U. S. Armed Forces M. J. **4:** 211, 1953.

[4] Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography. Philadelphia, Blakiston, 1951.

[5] Hullinghorst, R. L., and Steer, A.: Pathology of epidemic hemorrhagic fever. Ann. Int. Med. **38:** 77, 1953.

[6] Friedberg, C. K.: Diseases of the Heart. Philadelphia, Saunders, 1950. Pp. 834–852.

Postoperative Changes in the Electrocardiogram in Congenital Heart Disease

I. Pure Pulmonary Stenosis

By BERNHARD LANDTMAN, M.D.

Electrocardiograms of forty-six cases of pure pulmonary stenosis were analyzed before and after valvulotomy. The electrocardiograms taken at the last postoperative examinations (three months or longer after the operation) revealed significant changes as compared with the preoperative tracings. It is suggested that these changes may be due to the diminished load on the right ventricle and right auricle after the operation. Evidence is presented that electrocardiography offers a simple and valuable means for the evaluation of the result of valvulotomy in pure pulmonary stenosis.

SURGICAL advance in the correction of certain congenital cardiac defects renders an accurate diagnosis of these conditions important. In view of the fact that some malformations of the heart are associated with hypertrophy of the right ventricle whereas others are characterized by left-sided preponderance, a correct diagnosis often rests upon the evidence obtainable as to the relative amount of work demanded of these chambers. Consequently, the presence of right or left ventricular hypertrophy is one of the most important differential diagnostic signs. The difficulty, however, in the positive establishment of lesser degree of relative ventricular enlargement on clinical examination, including x-ray study, is well known and additional diagnostic procedures are often needed. Modern electrocardiography has increased the information derived from the electrocardiogram.

A considerable amount of statistical data has accumulated concerning the various intervals and deflections of the electrocardiogram in normal children.[1-7] The measurements obtained are, however, subject to a fairly wide range of variation which limits their value as normal standards in the study of specific cases.

From the Department of Pediatrics of the Johns Hopkins University, and the Cardiac Clinic of the Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md.

During recent years, certain electrocardiographic criteria for right and left ventricular hypertrophy have been established.[8-11] Most of these observations have been made on adult patients and, therefore, the measurements obtained are not directly applicable to the study of children. Moreover, there is still a lack of agreement as to which electrocardiographic measurement gives the most valuable information in regard to right and left ventricular hypertrophy.

Cardiac surgery offers an opportunity for a new approach to the electrocardiographic study of ventricular preponderance. The present study was undertaken in order to determine what changes, if any, occurred in the electrocardiogram of patients operated upon because of congenital heart disease. Only uncomplicated cases were included in this study. The material comprised malformations characterized by an increased load on the right ventricle as well as those with left ventricular preponderance. Furthermore, the types of malformations were selected so that the factor which caused the strain on the heart could be eliminated or at least greatly decreased by the operation. A comparison between the electrocardiograms taken before and after the operation, when either normal or practically normal conditions had been created, seemed to offer indirect evidence of the electrocardiographic patterns in right and left ventricular preponderance. The studies

TABLE 1.—*Forty-Six Cases of Pure Pulmonary Stenosis Studied before and after Pulmonary Valvulotomy*

Sex		Age in Yrs. at Time of Operation					Postoperative Observation Period in Mos.			
Males	Females	Under 1	1–5	6–10	11–15	16–25	3–6	7–12	13–24	25–48
18	28	2	12	17	9	6	11	14	12	9

were carried out in the Cardiac Clinic of the Harriet Lane Home in 1952.

THE REPORTED ELECTROCARDIOGRAM IN PURE PULMONARY STENOSIS

Pure pulmonary stenosis, according to modern nomenclature, refers to pulmonary stenosis with a closed ventricular septum.[12-14] Since pure pulmonary stenosis has only recently been recognized as a relatively common clinical entity, detailed studies of this malformation are comparatively few and there is still a lack of agreement as to the significant electrocardiographic changes.

Several investigators have commented on the frequent occurrence of right axis deviation in the standard leads in pure pulmonary stenosis.[14-20] Abrahams and Wood,[21] in a series of 60 cases, found right axis deviation in every case. Gøtzschke and his group,[22] on the other hand, reported right axis deviation in only 11 out of 21 cases of pure pulmonary stenosis all of which had been studied by cardiac catheterization. Likewise, Green and associates,[23] in a series of eight cases, observed right axis deviation in only two instances.

Several of these observers have noted that pure pulmonary stenosis is frequently associated with a high P wave in the electrocardiogram. Contrary to these reports, Dow and associates[24] recorded prominent P waves only once in a series of eight cases of this malformation.

Opinions still differ as to the diagnostic value of unipolar leads in pure pulmonary stenosis. Gøtzschke and associates,[22] in a series of 21 cases, claimed that these leads did not reveal any abnormal changes. Several investigators, on the other hand, have observed that pure pulmonary stenosis frequently shows signs of right ventricular hypertrophy in the precordial leads.[15, 21, 24-26] The main changes described are high R waves and inverted T waves in right ventricular surface leads.

Blackford and Parker,[27] in 1941, reported on a case of pure pulmonary stenosis in which the electrocardiogram showed complete right bundle-branch block. Subsequently, several investigators,[21, 23, 24, 28, 29] have commented on the occasional occurrence of complete or partial right bundle-branch block in pure pulmonary stenosis.

There are only very few reports on postoperative changes in the electrocardiogram in pure pulmonary stenosis. Brock and Campbell[30] presented tracings of a case, limited to the standard leads, in which an inverted T_2 became positive following pulmonary valvulotomy. Subsequently,[31] they reported on postoperative changes in the electrocardiograms in 11 cases of pure pulmonary stenosis. They stated that some transient changes, suggestive of muscular injury or pericarditis, were occasionally registered during the early postoperative period. Similar observations have been made by Soulié and associates[32] in a series of nine cases of pure pulmonary stenosis.

MATERIAL AND METHODS

The material comprised the electrocardiograms of 46 cases of pure pulmonary stenosis examined before and after valvulotomy (table 1). None of these patients has received digitalis or other drugs which might have affected the electrocardiogram.

All the electrocardiograms were taken under the same conditions with a Sanborn direct-writing cardiograph. The standard leads were recorded in the usual manner; unipolar precordial leads, V_1 through V_5, were taken using the central terminal of Wilson as indifferent electrode. Augmented unipolar extremity leads, aV_R, aV_L, and aV_F, were recorded according to the technic described by Goldberger.[8] Calibration corrections were applied, if necessary, for accurate standardization (10 mm. = 1 mv.). As a rule, at least three cardiac cycles were studied in each lead and from these the average measurements were derived in tabular form. A magnifying glass was often used to facilitate the study of individual measurements.

In each case the following electrocardiographic particulars were analyzed before and after the operation: Rate and rhythm were determined from any or all leads which were suitable. The duration

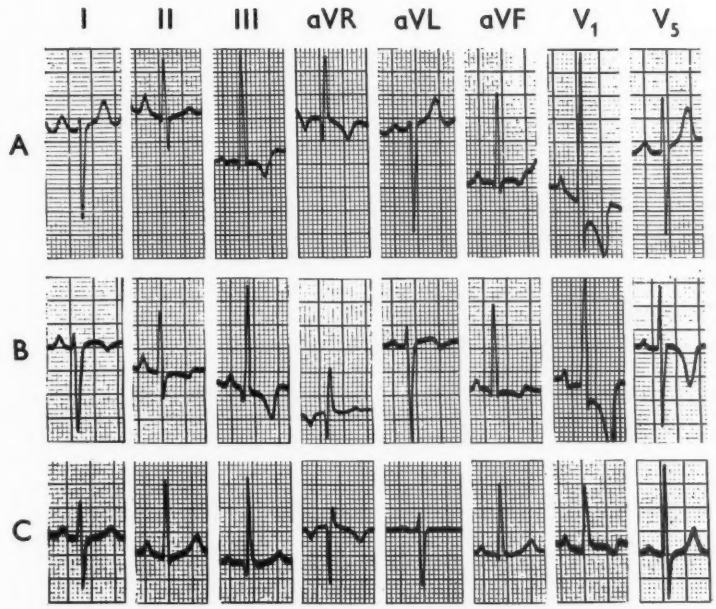


FIG. 1. *A*. Electrocardiogram of a girl, 9 years of age, with pure pulmonary stenosis. Marked right axis deviation. Peaked P wave in lead II. T-wave inversion in leads III, aV_R, aV_F, and V_1. Depression of the S-T segment in V_1. Cardiac catheterization revealed a right ventricular pressure of 200/10 mm. Hg. *B*. Two weeks after pulmonary valvulotomy. T-wave inversion, suggestive of myocardial injury, has appeared in leads I, II, aV_L, and V_5. These changes persisted for three additional weeks. *C*. One year after pulmonary valvulotomy. Note the decrease in the amplitude of the P wave in lead II and the decrease in the angle of the electrical axis. The T wave has become positive in leads I, II, III, aV_F and V_5. The R/Q and the R/S ratios have changed in aV_R, V_1 and V_5. At this time, the right ventricular pressure was 65/0 mm. Hg.

and the amplitude of the P wave, the P-R interval, the QRS duration and the Q-T interval were, according to standard procedures, obtained from standard lead II. The location of the electrical axis of the QRS complex was derived by algebraic addition from Einthoven's triangle. The relation between the electrical and the anatomic position of the heart was studied according to the criteria described by Wilson and associates.[11] The amplitudes of the Q, R, S and T waves were measured in the three standard leads, in the unipolar limb leads and in the right (V_1) and left (V_5) ventricular surface leads. The shape of the S-T segments was studied in all these leads. The onset of the intrinsicoid deflection in V_1 and in V_5 was measured from the beginning of the Q wave to the peak of the R wave. Finally, the ratio between the positive and negative deflection of the QRS complex was determined in all these leads.

According to this procedure, 60 electrocardiographic particulars were analyzed in each of the cases before and after the operation. The average pre- and postoperative measurements were derived from all groups. In the presentation of the results, only significant changes in the electrocardiograms will be discussed in detail.

The surgical technic consisted in each case of pulmonary valvulotomy. The operations were done by Dr. Blalock or by members of his surgical staff at the Johns Hopkins Hospital. At the operation, the stenosed valve was palpated in each instance and the typical jetlike thrill was felt distal to the stenosis.

Prior to the operation, 34 of the patients revealed slight cyanosis which disappeared after valvulotomy. This was considered to indicate the presence of a foramen ovale. The remainder of the patients were acyanotic before, as well as after, the operation.

Transient changes in the electrocardiogram, suggestive of myocardial injury or pericarditis, frequently occurred immediately after the operation, and these changes sometimes persisted during the subsequent few weeks. These changes, which were similar to those described by Brock and Campbell,[31] mainly affected the T waves. Figure 1 illustrates one of these cases. In addition, transient arrhythmias, mostly extrasystoles, were occasionally recorded

during the early postoperative period. Therefore, only those records of patients who had been followed for at least three months after the operation were included in this study. Table 1 shows that the postoperative observation period, that is, the time interval between the operation and the last postoperative electrocardiogram, was more than six months in 3 of the 46 cases. The average period was thirteen and one-half months.

TABLE 2.—*Average, Minimum and Maximum Duration and Amplitude of the P Wave, P-R Interval and QRS Duration in Forty-Six Cases of Pure Pulmonary Stenosis (A) before and (B) after Pulmonary Valvulotomy. The Measurements Were Derived from Lead II*

	P Wave						P-R Interval, sec.			QRS Duration, sec.		
	Amplitude, mv.			Duration, sec.								
	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.
A	0.324	0.10	0.70	0.082	0.05	0.11	0.151	0.09	0.23	0.073	0.05	0.11
B	0.190	0.05	0.30	0.070	0.05	0.10	0.150	0.09	0.21	0.069	0.04	0.10

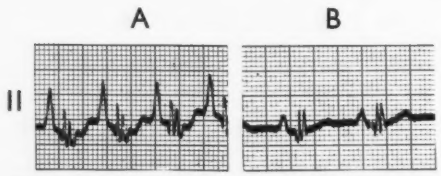


FIG. 2. *A*. Electrocardiogram (lead II) of a girl, 7 years of age, with pure pulmonary stenosis. High P wave, depression of the S-T segment and diphasic T wave. *B*. Two and a half years after pulmonary valvulotomy. Note the decrease in the amplitude of the P wave and the change to normal of the S-T segment and the T wave.

RESULTS OF PRESENT STUDY

Rhythm and Rate. Arrhythmias were not recorded in a single case before the operation or at the last postoperative examination. Prior to the operation, the average heart rate was 100.4 beats per minute. Following valvulotomy, a slight decrease in the heart rate was observed as a rule. The average rate was 90.1 beats per minute at the last examination.

P Wave, P-R Interval and QRS Duration. Following surgery, a significant decrease in the amplitude of the P wave was recorded in 40 of the 46 cases (table 2). Figure 2 illustrates a case in which the amplitude of the P wave in lead II decreased from 0.7 to 0.2 mv. A decrease in the duration of the P wave occurred after the operation in 33 instances. The average P-R interval and the average QRS duration showed no significant changes. Only occasionally was a significant decrease in the QRS duration recorded postoperatively (fig. 3). Table 2 shows that the different measurements were subject to a fairly wide range of variation before as well as after the operation.

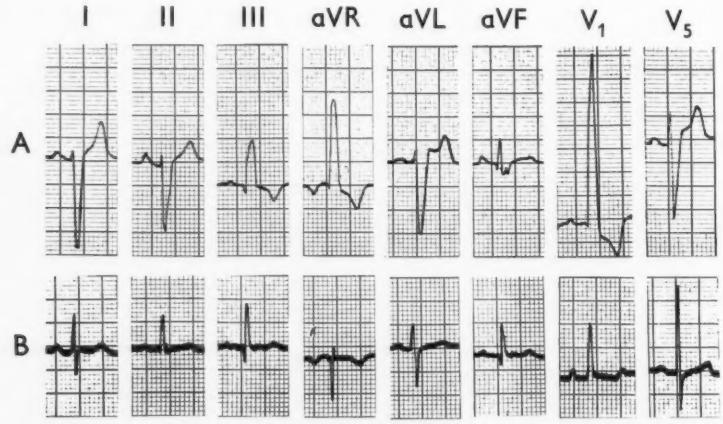


FIG. 3. *A*. Electrocardiogram of a girl, 15 years of age, with pure pulmonary stenosis. Marked right axis deviation. QRS duration of 0.10 second. S-T depression and delayed onset of the intrinsicoid deflection in V_1. *B*. Nine months after pulmonary valvulotomy. The electrical axis has become balanced. Note the decrease in the QRS duration. In V_1, the R wave and the S-T segment have changed towards normal. The R/Q and R/S ratios have changed in aV_R and V_5.

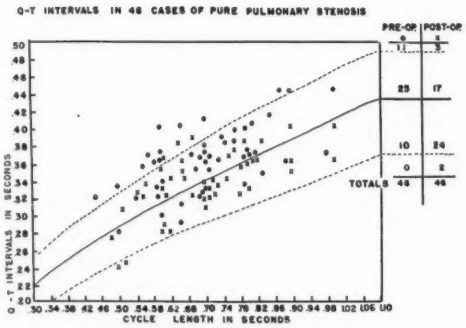


FIG. 4. The Q-T and R-R relationship (o) before and (x) after pulmonary valvulotomy were derived from Bazett's[33] formula Q-T = 0.404 $\sqrt{\text{R-R}}$. The middle curve represents the mean values of the corresponding Q-T intervals obtained by Alimurung and associates[34] in 517 normal children; the area covered by the dotted lines included 95.6 per cent of their cases.

TABLE 3.—*Electrical Axis of the QRS Complex and Electrical Position of the Heart in Forty-Six Cases of Pure Pulmonary Stenosis (A) before and (B) after Pulmonary Valvulotomy*

	Electrical Axis in Degrees					Electrical Position			
	60–90	91–120	121–150	151–180	−140	Vertical	Semi-vertical	Intermediate	Indeterminate
A	—	5	27	13	1	36	5	1	4
B	6	27	9	4	—	39	5	—	2

deviation was present in all the cases before the operation; the average angle was 134.5 degrees (table 3). Extreme right axis deviation, with negative main deflections in the three standard leads, was recorded in one case. There was a decrease in the angle of the electrical axis in 41 cases after the operation (figs. 1, 3, 6 and 7). The average postoperative angle was 110.3 degrees.

Prior to operation, the electrical position of the heart was vertical or semivertical in 41 of the cases (table 3). No significant change in the electrical position of the heart was recorded after the operation.

Q Wave. In most of the leads, no significant changes were seen in the amplitude of the Q wave. An isolated Q wave was present in lead I in six cases pre- and postoperatively. In lead II, a Q wave was recorded in 18 cases before and in 16 cases after the operation. Lead III showed a Q wave in 33 cases. With regard to the unipolar limb leads and the precordial leads significant changes in the Q waves were recorded postoperatively only in lead aV_R (figs. 1, 3, 5 and 6).

R Wave. Significant changes in the amplitude of the R waves were recorded in lead V_1 (table 4). Following pulmonary valvulotomy, a decrease in this measurement occurred in 40

TABLE 4.—*Average, Minimum and Maximum Amplitude of the R Wave in Millivolts in Forty-Six Cases of Pure Pulmonary Stenosis (A) before and (B) after Pulmonary Valvulotomy. Leads Showing Significant Postoperative Changes in the R Wave Are Presented.*

	I			III			aV_R			aV_F			V_1			V_5		
	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.
A	0.33	0	1.2	1.92	0.4	3.5	0.90	0	2.4	1.65	0.1	3.50	2.53	0.6	4.0	1.27	0.2	3.0
B	0.48	0	1.3	1.56	0.2	3.1	0.40	0	2.2	1.26	0.1	2.80	1.48	0.2	2.8	1.72	0.2	2.1

Q-T Interval. The Q-T intervals, plotted against the corresponding R-R measurements are presented in figure 4. The Q-T intervals were within normal limits in 35 cases and slightly increased in 11 cases. Following pulmonary valvulotomy, the Q-T interval decreased in 16 instances, the postoperative measurements being within normal range of variation in 41 instances.

Electrical Axis of the QRS Complex and Electrical Position of the Heart. Right axis

of the 46 cases. In most of the cases, there was a slight postoperative increase in the amplitude of the R waves in lead I and a corresponding decrease in lead III. No significant changes in the amplitude of the R waves were recorded in lead II or in aV_L. In lead aV_R and aV_F, on the other hand, a diminution in the amplitude of the R waves was recorded in the majority of the cases. In lead V_5, the average amplitude of the R wave slightly increased. Figures 1, 3, 5, 6 and 7 illustrate

FIG. 5. The shape of the QRS complex in aV_R in 46 cases of pure pulmonary stenosis (*A*) before and (*B*) after pulmonary valvulotomy. In lead aV_R, the R wave was greater than the Q wave in 41 patients before the operation. Note the decrease in the R/Q ratio after the operation. At the last postoperative examination the positive deflection of the QRS complex was greater than the negative in only 14 cases.

the changes in the R waves after the operation.

S Wave. There was as a rule a diminution in the amplitude of the S waves in lead I after the operation (average amplitudes 1.49 and 0.98 mv.). In lead III, an S wave was present in 10 cases before and in 6 cases after the operation. An S wave was recorded in lead II in 32 cases before and in 27 cases after the operation. The unipolar limb leads did not reveal any significant changes in the S waves. In aV_R, a separate S wave was not recorded in a single instance before or after the operation (fig. 5). S waves were present in all the cases in aV_L. Lead V_1 showed an S wave in only five cases before and after the operation. In V_5, an S wave was recorded in 42 cases before the operation. Following pulmonary valvulotomy, the amplitude of the S wave in V_5 decreased in 36 instances. Figures 1, 3, 6 and 7 illustrate the postoperative changes in the S waves.

R/S and R/Q Ratio. In many leads, changes in the ratio between the amplitude of the R wave and that of the main negative deflection were recorded after the operation. An increase in this ratio was usually seen in lead I and a corresponding decrease in lead III; this was consistent with the shift of the electrical axis towards the left. Significant changes also occurred in aV_R (figs. 1, 3, 5 and 6). Figure 5 shows that the positive deflection in aV_R was greater than the negative in 41 cases before the operation. Following pulmonary valvulotomy, this ratio decreased in 41 cases and in only 14 instances was the positive deflection bigger than the negative at the last examination. A postoperative increase in the R/S ratio in V_5 was recorded in 31 instances.

Onset of the Intrinsicoid Deflection. In lead V_1, the average time of onset of the intrinsicoid deflection before the operation was 0.048 second. A decrease in this measurement was recorded in 35 cases; the average postoperative measurement was 0.033 second. Lead V_5 did not show any changes in the time of onset of the intrinsicoid deflection; the average pre- and postoperative values were 0.024 second.

An rSR′ or RSR′ pattern in V_1, suggestive of partial right bundle-branch block, was recorded in five cases before the operation. Four of these cases showed evidence of patency of the foramen ovale. In three instances, an rSR′ or RSR′ pattern appeared in V_1 following pulmonary valvulotomy. Figure 6 illustrates one of these cases.

S-T Segment. The S-T segments were normal in all the leads in 8 of the 46 cases. Table 5 shows that the remaining patients presented S-T depression or strain in one or more leads. These changes were most frequently seen in leads III, aV_F and in V_1. Lead V_5 revealed changes in the S-T segments in four cases; in all of these, there was a marked clockwise rotation of the heart with right ventricular surface pattern recorded from V_1 through V_5. Following pulmonary valvulotomy, in 20 instances the S-T segments became normal in all the leads. Figures 1, 2, 3, 6 and 7 illustrate the changes of the S-T segments after the operation.

T Wave. Table 6 illustrates the direction of the T waves in the different leads before and after the operation. In lead I, a diminution in the amplitude of the T wave was recorded in 31 instances; the average pre- and postoperative measurements were respectively 0.287 and 0.197 mv. In V_1, the average amplitude of the T wave was −0.403 mv. Following surgery, the average amplitude was −0.360 mv.; thus, there was a slight decrease in the

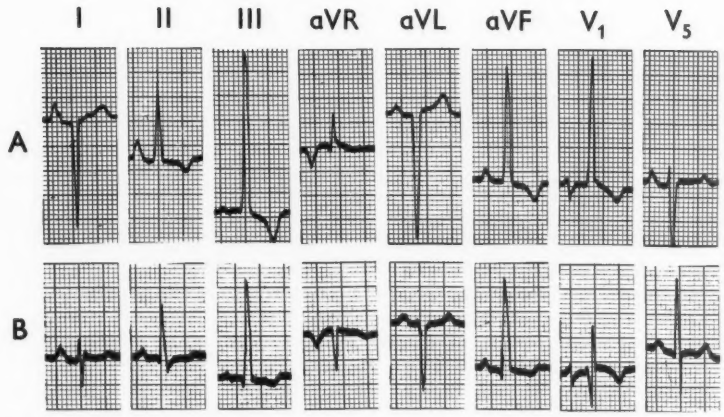


FIG. 6. *A*. Electrocardiogram of a boy, 8½ years of age, with pure pulmonary stenosis. Marked right axis deviation. High P wave in lead II. T-wave inversion in leads II, III, aV_F and V_1. *B*. Two years after pulmonary valvulotomy. Note the decrease in the angle of electrical axis, the diminished amplitude of the P wave in II, and the changes towards normal of the S-T segments and the T waves. Changes in the QRS complexes, suggestive of partial right bundle branch block, have appeared in lead I and V_1.

negativity of the T wave in this lead. Figures 1, 2, 3, 6 and 7 illustrate the postoperative changes in the T waves.

CLINICAL DATA

The exercise tolerance was within normal limits in four cases before the operation; the remainder of the patients showed varying degrees of incapacity. Following surgery, the exercise tolerance improved in 43 cases and at the last postoperative examination it was considered normal in 38 instances.

TABLE 5.—*The S-T Segments in Forty-Six Cases of Pure Pulmonary Stenosis (A) before and (B) after Pulmonary Valvulotomy*

	Normal S-T Segments in All Leads. No. of Cases	S-T Depression or Strain. No. of Cases							
		I	II	III	aV_R	aV_L	aV_F	V_1	V_5
A	8	—	10	23	9	—	16	36	4
B	28	—	2	6	4	1	4	12	4

The average preoperative systolic blood pressure was 105.5 mm. Hg. This pressure did not change. The diastolic blood pressure slightly decreased in 23 instances following pulmonary valvulotomy. The average pre- and postoperative diastolic blood pressures were 70.5 and 65.5 mm. Hg.

Cardiac catheterization was carried out in 30 cases preoperatively. In 26 cases the right ventricular systolic pressure exceeded 100 mm. Hg, the average systolic pressure being 144 mm. Hg. Twelve patients were recatheterized after the operation; in these cases the systolic pressure in the right ventricle had decreased by an average of 60.2 mm. Hg. There was a positive correlation between the degree of this pressure fall and the degree of the changes in the electrocardiogram (figs. 1 and 7).

The size of the heart, as determined by x-ray films, was within normal limits in 21

TABLE 6.—*Direction of the T Wave in Different Leads in Forty-Six Cases of Pure Pulmonary Stenosis (A) before and (B) after Pulmonary Valvulotomy*

Direction of T Wave	I		II		III		aV_R		aV_L		aV_F		V_1		V_5	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Positive	45	45	23	36	7	22	3	5	41	37	18	32	—	1	38	42
Isoelectric or diphasic	1	1	6	5	6	10	6	3	3	5	6	4	1	7	3	2
Negative	—	—	17	5	33	14	37	38	2	4	22	10	45	38	5	2

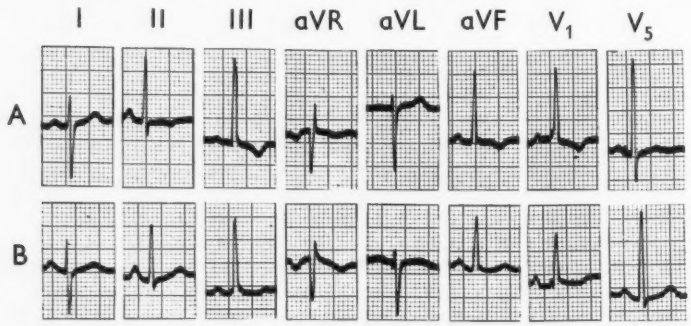


FIG. 7. *A*. Electrocardiogram of a girl, 13 years of age, with pure pulmonary stenosis. Right axis deviation. T-wave inversion in leads II, III, aV_F and V_1. Cardiac catheterization revealed a pressure in the right ventricle of 145/3 mm. Hg. *B*. Two years after pulmonary valvulotomy. The S-T segments and the T waves have changed towards normal. At this time, the pressure in the right ventricle was 115/5 mm. Hg.

cases before the operation. Cardiac enlargement, with a cardiothoracic ratio between 45 and 55 per cent, was present in 18 cases, and in seven cases the ratio exceeded 55 per cent. During the early postoperative period, an increase in the size of the heart often occurred. At the last postoperative examinations, 23 of the patients still revealed various degrees of cardiac enlargement. As compared with the preoperative measurements, the size of the heart had decreased in 19 cases; the most marked decrease usually occurred in the younger age groups. In 24 instances there was no obvious difference between the size of the heart before and after the operation. In three instances, the last examination showed that the heart had increased over its preoperative size. No significant relation was observed between the size of the heart and the degree of the postoperative changes in the electrocardiogram. Thus, in many instances, although after operation the size of the heart had remained unchanged, there was a marked change of the electrocardiogram towards normal combined with a fall in the right ventricular pressure.

DISCUSSION

Significant changes, which followed a uniform trend, were recorded in the electrocardiograms after pulmonary valvulotomy. Inasmuch as the electrocardiograms had remained unchanged on repeated preoperative examinations, the assumption is justified that the vast majority of these changes were a direct result of the operation on the heart.

A slight decrease in the heart rate occurred, as a rule, after the operation. This change may have been a direct effect of the valvulotomy on the heart action. The possibility, however, that the decrease in the heart rate was in part a physiologic phenomenon due to increasing age should also be borne in mind.

The average amplitude of the P wave before the operation was about twice as high as that described in normal children.[7] It is generally agreed that a high P wave suggests right auricular enlargement. The significant diminution in the amplitude of the P waves after the operation, the average measurement being within normal limits on the last postoperative examination, therefore, suggests a lessening of the load on the right auricle.

The Q-T interval was slightly increased in 14 cases before the operation, and a decrease in this measurement was recorded in 16 instances postoperatively. In this connection it is of interest that Alexander and associates[36] found the Q-T intervals to be within normal limits in 13 adult patients with right ventricular hypertrophy.

High R waves in proportion to the S waves in V_1 have been considered by many authors one of the most important electrocardiographic evidences of right ventricular hypertrophy.[9-11, 21, 35, 37] In the present study, the

average amplitude of the R waves in V_1 was about three times greater than that in normal children,[7] and an S wave was recorded in this lead in only five instances. Following pulmonary valvulotomy, a decrease in the amplitude of the R waves in V_1 was observed in 40 of the 46 cases. Indeed, the average amplitude of the R waves after the operation was about half of that before the operation. Therefore, it seems safe to assume that the decrease in the amplitude of the R waves in V_1 reflected the diminished load on the right ventricle after the operation.

In aV_R, the positive deflection of the QRS complex was greater than the negative deflection in 41 cases before the operation. It is worthy of note that Goodwin,[38] in a study of 53 healthy children, never observed the positive deflection to be greater than the negative deflection in aV_R. Children with right ventricular hypertrophy, on the other hand, frequently showed a relatively high R wave in this lead. Thus, although an R/Q ratio of more than unity in aV_R, according to a general concept,[8] merely indicates clockwise rotation of the heart, it appears to be a suggestive indirect sign of right ventricular preponderance. This assumption is supported by the fact that a significant decrease in the R/Q ratio in aV_R was observed in the majority of the cases after the operation.

Depression of the S-T segments and T-wave inversion in leads II and III, especially when combined with right axis deviation, have been considered signs of right ventricular hypertrophy according to a concept advanced by Barnes and Whitten.[39] In the present study, S-T depression or strain was recorded before the operation in the majority of the cases in leads II, III, aV_F or V_1. Following pulmonary valvulotomy, these changes usually disappeared, which suggests a diminished load on the right ventricle. The same applies to the T waves, which, prior to operation, were inverted in leads II, III and aV_F, and frequently became positive after the operation.

The upper limit of the time of onset of the intrinsicoid deflection V_1 in normal children is estimated at approximately 0.030 second.[7, 35, 40, 44] An increase in this measurement is considered by many investigators a strongly suggestive sign of right ventricular hypertrophy.[10, 11, 19, 37, 41] In the present study, the average time of onset of the intrinsicoid deflection in V_1 was 0.048 second. Following pulmonary valvulotomy, a decrease in this measurement was recorded in 35 instances. No corresponding changes were recorded in V_5 in which the onset of the RS deflection was within normal limits before the operation as well as postoperatively. This observation suggests that the left ventricular load, contrary to that of the right ventricle, was not diminished by the operation.

An rSR′ or RSR′ pattern in V_1, suggestive of partial right bundle-branch block, was recorded in five cases before the operation. Opinions still differ as to whether partial bundle-branch block, per se, represents a mild conduction defect or whether it is a sign of ventricular hypertrophy.[41-43] It is noteworthy that, in the present study, partial right bundle-branch block appeared in three cases following pulmonary valvulotomy. Since, in these cases, the electrocardiograms revealed evidence of a diminished load on the right ventricle combined with a fall in the right ventricular pressure, it seems reasonable to assume that the bundle-branch block which appeared after the operation was a conduction defect rather than a sign of ventricular hypertrophy.

As a rule, the postoperative changes in the electrocardiogram had stabilized about three months after pulmonary valvulotomy, and thereafter the tracings did not significantly change.

It is worthy of note that in a substantial number of the cases, the size of the heart did not diminish after surgery even in instances which showed a marked drop in the right ventricular pressure. The discrepancy between the marked clinical improvement and the failure of the heart to decrease in size following pulmonary valvulotomy has been observed by several investigators.[31, 32, 37] In the present study, the electrocardiograms as a rule revealed signs of diminished load on the right ventricle after the operation even in those cases in which the size of the heart had re-

mained unchanged. These findings indicate that electrocardiography is a sensitive method for measuring the degree of right ventricular strain. Therefore, comparative electrocardiograms taken before and after operation offer a simple and useful means for the evaluation of the result of valvulotomy in pure pulmonary stenosis.

Summary

Forty-six cases of pure pulmonary stenosis were studied before and after pulmonary valvulotomy. The majority of the patients were children. In each case, 60 electrocardiographic measurements were studied pre- and postoperatively.

The patients showed a uniform electrocardiographic pattern before the operation. Right axis deviation was present in all the cases. The electrical position of the heart was classified as vertical or semivertical in 41 instances. The average amplitude of the P waves was considerably greater than normal. The R waves in V_1 were high and delayed and S waves were present in this lead in only five instances. In aV_R, the R/Q ratio was greater than unity in 41 cases. Normal S-T segments in all the leads were recorded in only eight cases; the remainder of the patients showed S-T depression in one or more leads. These changes were most frequently seen in leads II, III, aV_F and V_1. In addition, these leads frequently showed T-wave inversion.

After pulmonary valvulotomy, transient changes in the electrocardiogram, mainly T-wave inversion and extrasystoles, suggestive of myocardial or pericardial involvement, frequently occurred during the early postoperative period.

The electrocardiograms taken at the last postoperative examinations (three months to four years after the operation) revealed significant changes as compared with the preoperative tracings.

A slight decrease was recorded in the average heart rate.

The amplitude of the P waves diminished in 40 instances. A decrease in the duration of the P wave occurred in 33 instances.

The Q-T interval decreased slightly in 16 cases.

A decrease in the angle of the electrical axis occurred in 41 instances.

The amplitude of the R waves in V_1 decreased in 40 cases. In three instances signs of partial right bundle-branch block appeared after the operation. In V_1, the onset of the intrinsicoid deflection diminished in 35 cases.

The R/Q ratio in aV_R decreased in 41 cases. In V_5 an increase in the R/S ratio was recorded in 31 instances.

The S-T segments frequently became normal in leads II, III, aV_F and V_1; in these leads, the T waves frequently became positive.

The postoperative changes measured in the electrocardiogram were considered to be due to the diminished load on the right side of the heart.

The size of the heart frequently remained unchanged after surgery even in cases which showed significant changes in the electrocardiogram towards normal and a marked postoperative drop in the right ventricular pressure.

Sumario Español

Cuarenta y seis casos de estenosis pulmonar pura fueron estudiados antes y después de valvulotomía pulmonar. La mayoría de los casos fueron niños. En cada caso, 60 medidas electrocardiográficas fueron estudiadas antes y después de la operación.

Los pacientes mostraron un patrón electrocardiográfico uniforme antes de la operación. Desviación del eje estuvo presente en todos los casos. La posición eléctrica del corazón clasificada como vertical o semivertical en 41 casos. La amplitud promedio de la onda P fué considerablemente más grande que lo normal. Las ondas R en V_1 fueron altas y tardías y las ondas S estuvieron presentes en esta derivación en solo cinco casos. En aV_R, la proporción R/Q fué mayor que unidad en 41 casos. Segmentos S-T normales en todas las derivaciones fueron registrados en solamente ocho casos; el restante de pacientes mostraron depresión del segmento S-T en una o más derivaciones. Estos cambios fueron más frecuentemente ob-

servados en las derivaciones II, III, aV_F y V_1. En adición estas derivaciones frecuentemente mostraron inversión de las ondas T.

Luego de la valvulotomía pulmonar en el período temprano postoperatorio se observaron cambios transitorios en el electrocardiograma, principalmente inversión de las ondas T y extrasístoles, sugestivos de daño al miocardio o pericardio.

Los electrocardiogramas tomados en el último examen postoperatorio (de tres meses a cuatro años después de la operación) revelaron cambios significativos al ser comparados con los trazados preoperatorios.

Un pequeño decremento en la frecuencia del pulso se registró en promedio.

La amplitud de las ondas P disminuyó en 40 casos. Un decremento en la duración de la onda P ocurrió en 33 casos. El intervalo Q-T disminuyó ligeramente en 16 casos. Un decremento en el ángulo del eje eléctrico ocurrió en 41 casos. La amplitud de las ondas R en V_1 disminuyó en 40 casos. En tres casos hallazgos de bloqueo parcial de rama derecha aparecieron luego de la operación. El comienzo de la desviación intrinsecoide en V_1 disminuyó en 35 casos.

La proporción R/Q en aV_R disminuyó en 41 casos. En V_5 un incremento en la proporción R/S se registró en 31 casos.

Los segmentos S-T frecuentemente se normaizlaron en las derivaciones II, III, aV_F y V_1; en estas derivaciones, las ondas T frecuentemente se tornaron positivas.

Los cambios postoperatorios determinados en el electrocardiograma fueron considerados ser causados por la disminución en el trabajo del lado derecho del corazón.

El tamaño del corazón frecuentemente permaneció inalterado después de la operación aún en los casos que mostraron cambios significativos en el electrocardiograma hacia lo normal y una marcada disminución en la presión del ventrículo derecho.

Acknowledgment

I wish to express my gratitude to Dr. Helen B. Taussig, Physician-in-Charge of the Harriet Lane Home Cardiac Clinic, for placing at my disposal the unique material of the Clinic, and for the help and stimulating criticism rendered throughout this study.

References

[1] Alimurung, M. M., Lester, G. J., Nadas, A. S. and Massell, B. F.: The unipolar precordial and extremity electrocardiogram in normal infants and children. Circulation **4:** 420, 1951.

[2] Battro, A., and Mendy, J. C.: Precordial leads in children. Arch. Int. Med. **78:** 31, 1946.

[3] Mannheimer, E.: Calibrated phonocardiography and electrocardiography. Acta Paediat. **28:** Suppl. 2, 1940.

[4] Maroney, M., and Rantz, L. A.: Electrocardiogram in 679 healthy infants and children. Pediatrics **5:** 398, 1950.

[5] Switzer, J. L., and Besoin, M.: Electrocardiograms of normal children with special reference to the aV limb leads and chest leads. Am. J. Dis. Child. **79:** 449, 1950.

[6] Yu, P. N. G., Joos, H. A., and Katsampes, C. P.: Unipolar electrocardiogram in normal infants and children. Am. Heart J. **41:** 91, 1951.

[7] Ziegler, R. F.: Electrocardiographic studies in normal infants and children. Springfield, Ill., Charles C Thomas, 1951.

[8] Goldberger, E.: Unipolar lead electrocardiography. Philadelphia, Lea & Febiger, 1949.

[9] Myers, G. B., Klein, H. A., and Stofer, B. E.: The electrocardiographic diagnosis of right ventricular hypertrophy. Am. Heart J. **35:** 1, 1948.

[10] Sokolow, M., and Lyon, P.: The ventricular complex in right ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am. Heart J. **38:** 273, 1949.

[11] Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliviera, R. M., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[12] Blalock, A., and Kieffer, R. F., Jr.: Valvulotomy for the relief of congenital valvular pulmonic stenosis with intact ventricular septum. Ann. Surg. **132:** 496, 1950.

[13] Brock, R. C.: Congenital pulmonary stenosis. Am. J. Med. **12:** 66, 1952.

[14] Taussig, H. B.: Congenital Malformations of the Heart. New York, Commonwealth Fund, 1947.

[15] Allanby, K. D., and Campbell, M.: Congenital pulmonary stenosis with closed ventricular septum. Guy's Hosp. Rep. **98:** 18, 1949.

[16] Currens, J. H., Kinney, T. D., and White, P. D.: Pulmonary stenosis with intact interventricular septum. Am. Heart J. **30:** 491, 1945.

[17] Joly, F., Folly, G., and Carlotti, J.: Étude électrocardiographique comparée des trilogies et tétralogies de Fallot. Arch. mal coeur **12:** 1108, 1952.

[18] Mannheimer, E., Larsson, Y., Möller, T., Lageröf, H., and Werkö, L.: Congenital iso-

lated pulmonary stenosis. A clinical study of seven cases diagnosed by heart catheterization. Acta Paediat. **38:** 484, 1949.

[19] Oglesby, P., Myers, G. S., and Campbell, J. A.: The electrocardiogram in congenital heart disease. Circulation **3:** 564, 1951.

[20] Selzer, A., Carnes, W. H., Noble, C. A., Higgins, W., and Holmes, R. O.: The syndrome of pulmonary stenosis with patent foramen ovale. Am. J. Med. **6:** 3, 1949.

[21] Abrahams, D. G., and Wood, P.: Pulmonary stenosis with normal aortic root. Brit. Heart J. **13:** 519, 1951.

[22] Gøtzschke, H., Eskildsen, P., and Tybjaerg Hansen, A.: Isolated pulmonary stenosis. Acta Med. Scandinav. **139:** 431, 1951.

[23] Green, D. G., Baldwin, E., Baldwin, J. S., Himmelstein, A., Roh, C. E., and Cournand, A.: Pure congenital pulmonary stenosis and idiopathic congenital dilatation of the pulmonary artery. Am. J. Med. **6:** 24, 1949.

[24] Dow, J. W., Levine, H. D., Elkin, M., Hayes, F. W., Hellems, H. K., Whittenberger, J. W., Ferris, B. G., Goodale, W. T., Harvey, W. P., Eppinger, E. C., and Dexter, L.: Studies of congenital heart disease. IV. Uncomplicated pulmonic stenosis. Circulation **1:** 267, 1950.

[25] Johnson, R. P., and Johnson, E. E.: Congenital pulmonic stenosis with open foramen ovale in infancy. Am. Heart J. **44:** 244, 1949.

[26] Taussig, H. B.: Diagnosis and management of common malformations of the heart. Circulation **6:** 6, 1952.

[27] Blackford, L. M., and Parker, F. P.: Pulmonary stenosis with bundle branch block. Arch. Int. Med. **67:** 1107, 1941.

[28] Durand, M., and Metianu, C.: Présentation d'un cas de sténose congénitale pure de l'orifice pulmonaire avec vérification anatomique. Arch. mal coeur **42:** 1112, 1949.

[29] Engle, M. A., and Taussig, H. B.: Valvular pulmonic stenosis with intact ventricular septum and patent foramen ovale. Circulation **2:** 481, 1950.

[30] Brock, R. C., and Campbell, M.: Infundibular resection or dilatation for infundibular stenosis. Brit. Heart J. **12:** 403, 1950.

[31] —, and —: Valvulotomy for pulmonary stenosis. Brit. Heart J. **12:** 377, 1950.

[32] Soulié, P., Joly, F., Carlotti, J., Sicot, J. R., and Voci, G.: Étude physiopathologique postopératoire de la trilogie de Fallot (Étude de neuf cas après valvulotomie pulmonaire). Arch. mal coeur **5:** 385, 1952.

[33] Bazett, H. C.: An analysis of the time-relations of electrocardiograms. Heart **7:** 354, 1920.

[34] Alimurung, M. M., Lester, G. J., Graige, E., and Massell, B. F.: The Q-T interval in normal infants and children. Circulation **1:** 1329, 1950.

[35] Veasy, G., and Adams, F. H.: Unipolar lead electrocardiography in children. Pediatrics **9:** 395, 1952.

[36] Alexander, J. K., Ferrer, M. I., Harvey, R. M., and Cournand, A.: The Q-T interval in chronic cor pulmonale. Circulation **3:** 733, 1951.

[37] Taussig, H. B.: Personal communication.

[38] Goodwin, J. F.: The electrocardiogram in normal children and in children with right ventricular hypertrophy. Brit. Heart J. **14:** 173, 1952.

[39] Barnes, A. R., and Whitten, M. B.: Study of T wave negativity in predominant ventricular strain. Am. Heart J. **5:** 14, 1929.

[40] Pagnoni, A., and Goodwin, J. F.: The cardiographic diagnosis of combined ventricular hypertrophy. Brit. Heart J. **14:** 451, 1952.

[41] Cosby, R. S., Levinson, D. C., Zinn, W. J., Dimitroff, S. P., and Griffith, G. C.: Congenital heart disease: An analysis of electrocardiographic patterns in forty-four patients with elevated right ventricular pressure. Am. Heart J. **44:** 581, 1952.

[42] Barker, J. M., and Valencia, F.: The precordial electrocardiogram in incomplete right bundle branch block. Am. Heart J. **38:** 376, 1946.

[43] Laham, J., Gialloreto, O., and Lenegre, J.: Electrocardiographic analysis of ventricular hypertrophy in bundle branch block. Acta cardiol. **6:** 129, 1951.

[44] Tudbury, P. B., and Atkinson, D. W.: The electrocardiograms of one hundred normal infants and children. J. Pediat. **36:** 446, 1950.

Postoperative Changes in the Electrocardiogram in Congenital Heart Disease

II. Coarctation of the Aorta and Patent Ductus Arteriosus

By Bernhard Landtman, M.D.

Electrocardiograms of 41 cases of coarctation and of 73 cases of patent ductus arteriosus were analyzed before and after surgical correction of the defect. The changes in the electrocardiogram which occurred after surgical repair of the coarctation were considered to be due to the diminished load on the left ventricle. In 65 of the cases of patent ductus arteriosus, electrocardiographic signs of left ventricular hypertrophy were recorded. Eight patients, seven of whom presented atypical murmurs, showed evidence of right ventricular or combined ventricular hypertrophy. Following ligation of the ductus, the electrocardiogram became normal in the majority of the cases.

In a previous communication,[1] postoperative changes in the electrocardiogram were presented in 46 cases of pure pulmonary stenosis. The electrocardiographic changes which occurred after valvulotomy were considered due to the diminished load on the right ventricle and right auricle.

The present report deals with corresponding changes in the electrocardiogram in coarctation of the aorta and in patent ductus arteriosus. In each case, 60 electrocardiographic measurements were analyzed before and after the operation. The methods have been described in the first part of the study.[1] Again, in the presentation of the results, only significant changes in the electrocardiogram will be discussed in detail.

Coarctation of the Aorta

The Reported Electrocardiogram in Coarctation of the Aorta

There is no uniform agreement as to the electrocardiographic changes produced by coarctation of the aorta. According to some observers, the electrocardiogram is usually normal in coarctation and, therefore, of little help in the recognition of this malformation.[2-6] Several authors have, however, commented on the frequent occurrence of left axis deviation in the standard leads in coarctation.[7-11] Rhodes and Durbin,[12] in a group of 116 patients of all ages, reported left axis deviation in 57 instances.

Since the advent of unipolar electrocardiography, evidence has been presented that coarctation occasionally shows left ventricular hypertrophy pattern in the precordial leads. Sokolow and Edgar,[13] in a study of 32 cases, found electrocardiographic signs of left ventricular hypertrophy in 19 instances. Likewise, Oglesby and associates[14] reported that in 8 out of 11 cases of coarctation the precordial leads showed left ventricular hypertrophy pattern. Alimurung and Smith[15] came to similar conclusions in an electrocardiographic study of 10 cases of coarctation. Most of these observations were made on adult patients and no details were given as to the electrocardiographic criteria of left ventricular hypertrophy or strain employed.

Most investigators agree that right axis deviation very rarely occurs in coarctation unless there are additional cardiovascular anomalies[13, 16, 17] or signs of heart failure.[18]

Solitary cases of coarctation which showed right bundle-branch block in the electrocardiogram have been reported by different observers.[13-15, 19]

The writer has failed to find reports in the literature on postoperative studies of the electrocardiogram in coarctation of the aorta.

From the Department of Pediatrics of the Johns Hopkins University, and the Cardiac Clinic of the Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md.

TABLE 1.—*Average, Minimum and Maximum Duration and Amplitude of the P Wave, P-R Interval and QRS Duration in 41 Cases of Coarctation of the Aorta (A) before and (B) after Surgical Correction of the Coarctation. The Measurements Were Derived from Lead II*

	P Wave						P-R Interval, sec.			QRS Duration, sec.		
	Amplitude, mv.			Duration, sec.								
	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.
A	0.130	0.05	0.30	0.085	0.06	0.12	0.153	0.11	0.20	0.073	0.05	0.10
B	0.112	0.05	0.20	0.075	0.05	0.10	0.147	0.11	0.20	0.069	0.05	0.09

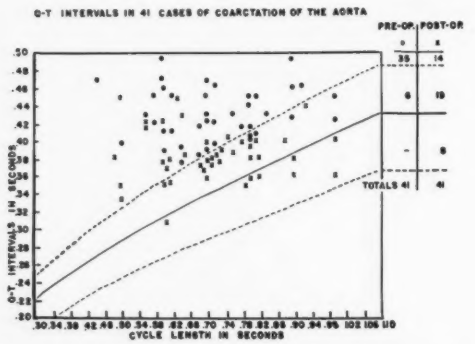


FIG. 1. The Q-T intervals were derived from Bazett's[20] formula Q-T = 0.404 $\sqrt{\text{R-R}}$. Prior to operation (o), in 35 instances, the Q-T interval was above the range of variation as described in normal children.[21] Following surgical correction of the coarctation, the Q-T interval decreased in 35 cases. In 27 instances, the Q-T interval was within normal limits at the last examination (x).

Material

The material comprised the electrocardiograms of 41 cases of uncomplicated coarctation of the aorta. There were 27 males and 14 females. The age of the patients ranged between 5 and 25 years. Thirty-seven of the patients were under 15 years of age at the time of the operation. The time interval between the operation and the last postoperative electrocardiogram ranged between three months and five years. In 31 cases the period of observation exceeded six months (average 15½ months).

The operations were done by Dr. Blalock or by members of his surgical staff at the Johns Hopkins Hospital. In 37 cases, the surgical technic consisted of resection of the coarctation and end-to-end aortic anastomosis. In the four remaining cases, the coarctation was too long to permit such a procedure. In three of these cases, an anastomosis was created between the left subclavian artery and the aorta beyond the obstruction. In one case, after resection of the coarctation, an arterial homograft was inserted between the proximal and distal segments of the aorta.

Results of Present Study

Rhythm and Rate. A normal sinus rhythm was recorded in 40 of the cases. Prior to operation, one patient showed occasional extrasystoles; following surgery, the rhythm became normal. In some instances, arrhythmias, mostly extrasystoles, were recorded as transient phenomena during the early postoperative period. In one case occasional extrasystoles were recorded at the last postoperative examination.

Prior to operation, the average heart rate was 90.3 beats per minute. Following surgery, a slight decrease in the heart rate occurred in most of the cases. At the last postoperative examination, the average rate was 82.2 beats per minute.

P Wave, P-R Interval and QRS Duration. The pre- and postoperative measurements are summarized in table 1. In 17 cases a slight decrease occurred in the amplitude and the duration of the P wave after the operation. No significant changes were seen in the average P-R interval or in the QRS duration.

Q-T Interval. Figure 1 illustrates the Q-T intervals before and after surgical correction of the coarctation. In 35 of the cases, the Q-T interval was above the normal range of variation. Following surgery, a decrease in the Q-T interval was recorded in 35 instances. At the last postoperative examination, the interval was within normal limits in 27 cases.

Electrical Axis of the QRS Complex and Electrocardiographic Position of the Heart. Prior to operation, a balanced axis was present in 25 of the cases. Left axis deviation, which ranged between −60 and +30 degrees, was recorded in 14 instances. Two patients showed right axis deviation. For the entire group, the average angle of the electrical axis was 15 degrees. Following operation, an increase in the angle was recorded in 22 instances. At the last postoperative examination the average angle was 23.2 degrees. At this time, left axis deviation was present in nine and right axis deviation in two instances.

Prior to operation, the electrocardiographic position of the heart was vertical or semivertical in 22 cases and horizontal or semihorizontal in 10 cases. An intermediate position was present in seven cases. In two instances, the position was indeterminate. Following surgery, in nine cases, the heart assumed a vertical or semivertical electrical position. At the last postoperative examination, a vertical or semivertical position was recorded in 31 cases and a horizontal or semihorizontal in five instances.

Q Wave. No significant changes were seen in the incidence or in the amplitude of the Q waves in the different leads. Lead I showed a Q wave in 14 cases. In lead II, the corresponding figure was 20. In lead III, a Q wave was present in 16 cases before and in 22 cases after the operation. None of the cases showed a Q wave in lead V_1. In V_5, a Q wave was recorded in 31 cases before and in 33 cases after the operation.

R Wave. Significant changes in the R waves were recorded in lead V_5 (table 2). Following operation, a decrease in this measurement occurred in 35 instances. In leads I, II and aV_L, a slight decrease in the amplitude of the R wave occurred in 28 instances. The other leads did not reveal any significant changes in the R waves. Figures 2 to 4 illustrate the postoperative changes in the R waves in the different leads.

TABLE 2.—*Average, Minimum and Maximum Amplitude of the R Wave in Millivolts in 41 Cases of Coarctation of the Aorta (A) before and (B) after Surgical Correction of the Coarctation. Leads Showing Significant Postoperative Changes in the R Wave Are Presented*

	I			II			aV_L			V_5		
	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.
A	1.32	0.20	2.10	1.45	0.40	2.20	0.66	0.10	1.50	2.51	1.20	3.80
B	0.93	0.20	2.00	1.28	0.40	2.20	0.46	0.10	1.30	1.88	0.80	3.00

S Wave. In lead III, a decrease in the amplitude of the S wave was recorded in 24 cases; the average pre- and postoperative measurements were 0.31 and 0.20 mv. A slight decrease in the average amplitude of the S wave was also recorded in leads II (from 0.32 to 0.18 mv.), in aV_F (from 0.22 to 0.16 mv.) and in V_1 (from 1.51 to 1.15 mv.).

R/S and R/Q Ratio. Following surgery, a decrease in the R/S ratio in lead I and a corresponding increase in this ratio in lead III was recorded in the majority of the cases. This was consistent with the slight shift of the electrical axis towards the right. In V_1, the R/S ratio was less than unity in all the cases; an

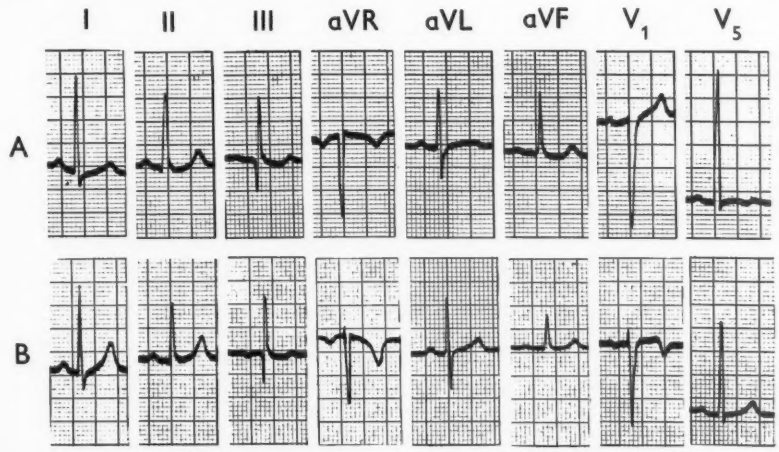


FIG. 2. *A*. Electrocardiogram of a male, 21 years of age, with coarctation of the aorta. Slight depression of the S-T segments in leads I, II and aV_F. Diphasic T wave in V_5. The blood pressure was 190/100 mm. Hg. *B*. Twelve months after surgical correction of the coarctation. The S-T segments have become normal. In V_5, time of onset of the intrinsicoid deflection has decreased, and the T wave has become positive. The blood pressure was 130/80 mm. Hg.

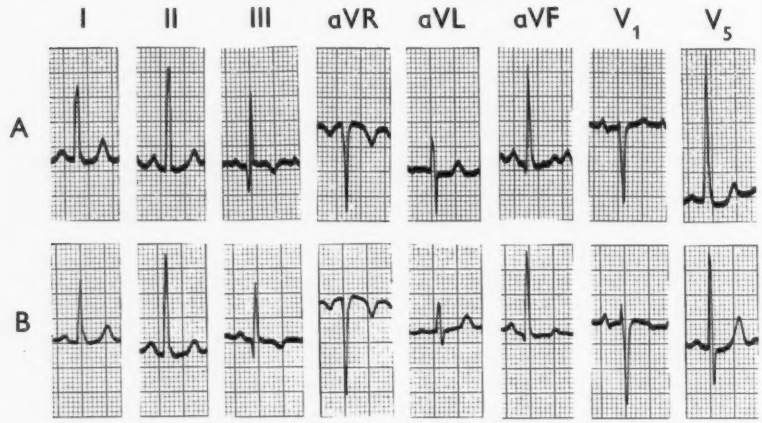


FIG. 3. *A*. Electrocardiogram of a girl, 8 years of age, with coarctation of the aorta. Slight depression of the S-T segments in leads I, II, aV_L and V_5. The blood pressure was 165/80 mm. Hg. *B*. Three months after surgical correction of the coarctation. The S-T segments have changed towards normal. In V_5 the time of onset of the intrinsicoid deflection and the amplitude of the R wave have decreased. The blood pressure was 125/85 mm. Hg.

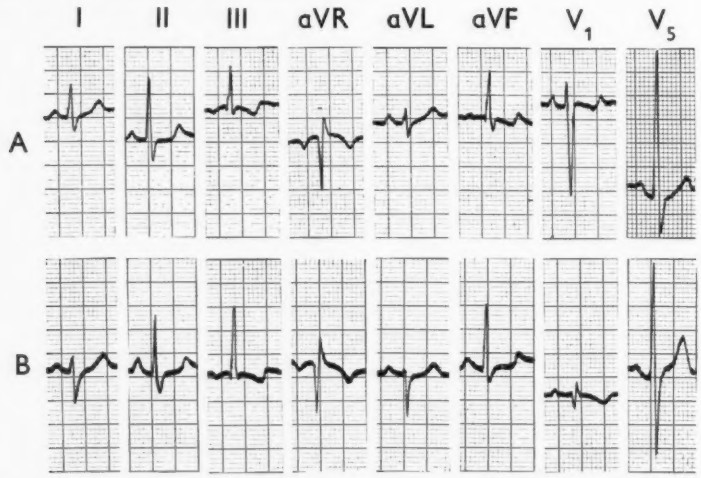


FIG. 4. *A*. Electrocardiogram of a girl, 13 years of age, with coarctation of the aorta. Slight depression of the S-T segments in leads II, aV_F and V_5. The blood pressure was 180/100 mm. Hg. *B*. Nine months after surgical correction of the coarctation. Note the shift of the electrical axis towards right. The S-T segments have changed towards normal. A rSR′ pattern has appeared in V_1. In V_5, the amplitude of the R wave has diminished, and the time of onset of the intrinsicoid deflection has decreased. The blood pressure was 100/60 mm. Hg.

increase in this ratio was recorded in 28 instances. In V_5, the R/S ratio was greater than unity in all the cases. Following surgery a decrease in this ratio was recorded in 27 cases. It is worthy of note that in aV_R the amplitude of the R wave never exceeded that of the main negative deflection. In this lead, 20 of the cases showed a QS pattern (figs. 2 and 3). An isolated Q wave was present in 16 cases (figs. 4 and 5) and a separate S wave in five instances.

Onset of the Intrinsicoid Deflection. Prior to operation, lead V_1 showed an average time of onset of the RS deflection of 0.018 second; this

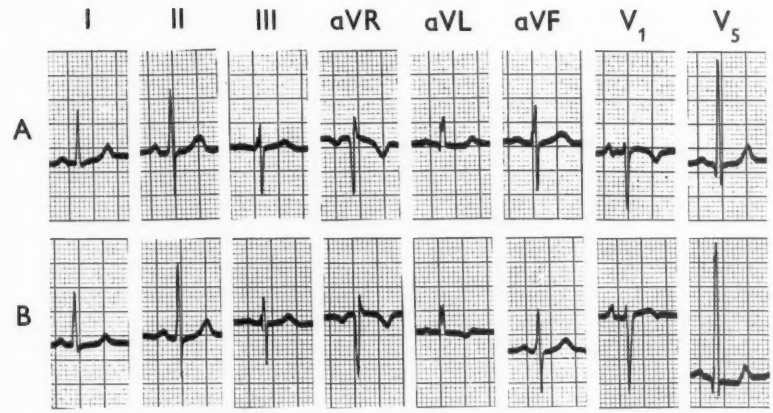


FIG. 5. *A*. Electrocardiogram of a girl, 10 years of age, with coarctation of the aorta. Left axis deviation; horizontal position. The blood pressure was 165/100 mm. Hg. In this case, the coarctation was too long to enable resection of the coarctation and end-to-end aortic anastomosis. Therefore, an anastomosis was created between the left subclavian artery and the descending aorta beyond the coarctation. The blood pressure, however, did not change after the operation. *B*. Nineteen months after the operation. Note the appearance of signs of left ventricular hypertrophy. Slight depression of the S-T segments in leads I, aV_L and V_5. In V_5, the amplitude of the R wave has increased.

TABLE 3.—*The S-T Segments in Different Leads in 41 Cases of Coarctation of the Aorta (A) before and (B) after Surgical Correction of the Coarctation*

	Normal S-T Segments in All the Leads. No. of Cases	S-T Depression or Strain. No. of Cases							
		I	II	III	aVR	aVL	aVF	V_1	V_5
A	20	5	9	4	—	—	5	1	10
B	31	1	2	4	—	—	3	1	3

measurement did not change. An rSR′ or RSR′ pattern in V_1, suggestive of partial right bundle-branch block, was recorded in three cases before and in four cases after the operation. In lead V_5, the average time of onset of the intrinsicoid deflection was 0.035 second. Following surgery, this measurement diminished in 34 cases; the average measurement was 0.029 second at the last postoperative examination (figs. 2 to 4).

S-T Segment. Prior to operation, the S-T segments were normal in all the leads in 20 of the 41 cases (table 3). The remaining patients revealed S-T depression or strain in one or more leads. These changes were most frequently seen in leads V_5, II, I and aV_F. Following operation, in 11 cases the S-T segments became normal. Figures 2–4 show the postoperative changes in the S-T segments.

T Wave. The T waves were normal in the majority of the cases. Table 4 shows that the T waves were consistently positive in lead I and only exceptionally negative or diphasic in leads II, aV_L and V_5. No significant changes occurred in the direction or in the average amplitude of the T waves after the operation.

Clinical Data

None of the patients showed signs of heart failure. Prior to operation, the average systolic pressure was 166 mm. Hg. In 32 cases, the systolic pressure exceeded 150 mm. Hg. Following surgical correction of the coarctation a decrease in the systolic blood pressure was recorded in 40 instances; the average systolic reading was 126.1 mm. Hg at the last examination. Prior to operation the average diastolic blood pressure was 99.3 mm. Hg. Following surgery, the diastolic pressure decreased in 38 instances. At the last postoperative examination the average diastolic pressure was 77.7 mm. Hg. Prior to surgery, the blood pressure was obtainable in the legs in only eight cases. Following surgery, the blood pressure was recorded in the legs in all the cases, the average systolic pressure at the last examination being 130.1 mm. Hg.

TABLE 4.—*The Direction of the T Wave in Different Leads in 41 Cases of Coarctation of the Aorta (A) before and (B) after Surgical Correction of the Coarctation*

Direction of the T Wave	I		II		III		aV_R		aV_L		aV_F		V_1		V_5	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Positive	41	41	38	38	12	15	—	—	38	38	31	37	10	11	37	40
Isoelectric or diphasic	—	—	1	2	10	10	—	—	3	3	7	2	6	4	2	1
Negative	—	—	2	1	19	16	41	41	—	—	3	2	25	26	2	—

There was a positive correlation between the postoperative fall in the blood pressure and the degree of the changes in the electrocardiogram towards normal (figs. 2 to 5).

The size of the heart, as determined by x-ray, was within normal limits in 32 cases. The remaining patients showed slight or moderate cardiac enlargement. Following surgery, the size of the heart decreased in 13 cases. At the last examination, seven patients still revealed slight cardiac enlargement. No significant correlation was seen between the size of the heart and the degree of the postoperative changes in the electrocardiogram.

PATENT DUCTUS ARTERIOSUS

The Reported Electrocardiogram in Patent Ductus Arteriosus

Many investigators agree that the electrocardiogram is normal in the majority of patients with uncomplicated patent ductus arteriosus.[9, 22-27] More recently, however, evidence has been brought forward that patent ductus arteriosus may occasionally show signs of left ventricular hypertrophy in the precordial leads.[28-34] Sokolow and Edgar,[13] in a study of 39 cases, found electrocardiographic evidence of left ventricular hypertrophy in the precordial leads in 17 instances. The main changes described are high and delayed R waves and inversion of the T waves in left ventricular surface leads.

It has been said that the presence of electrocardiographic evidence of right ventricular hypertrophy is so rare in patent ductus arteriosus as practically to exclude an uncomplicated lesion.[25, 34, 35] Gross,[36] in a series of 526 cases, found right ventricular preponderance in the electrocardiogram in only six instances. Occasionally, however, patent ductus arteriosus may show electrocardiographic evidence of right ventricular or combined ventricular hypertrophy especially in young infants and in patients with pulmonary hypertension.[28, 29, 37-39]

Cabrera and his associates,[40] in 1952, reported on postoperative changes in the electrocardiogram in 33 cases of patent ductus arteriosus. Changes such as a decrease in the duration of the P wave, diminution of the amplitude of the R and the T waves in lead V_5, and changes in the S-T segments were recorded in a number of cases. In many instances, the electrocardiograms were taken a few hours after the operation; in the entire group the average period of observation was only 30 days.

Solitary cases of patent ductus arteriosus which showed postoperative changes in the electrical axis in the standard leads have been reported by different authors.[9, 24, 41]

Material

Electrocardiograms of 73 cases of uncomplicated patent ductus arteriosus were included in the study. There were 28 males and 45 females. At the time of the operation, the age of the patients ranged between 5 months and 28 years. Sixty-two of the patients were under 10 years of age.

In all the cases, the ductus was closed by means of the suture ligation technic described by Blalock.[42]

The time interval between the operation and the last postoperative electrocardiogram ranged between three months and five years. In 55 cases the time interval exceeded six months (average 14 months).

Results of Present Study

Rhythm and Rate. Prior to operation, 70 of the patients showed a normal sinus rhythm. Occasional extrasystoles were recorded in three instances. Transient arrhythmias, mostly extrasystoles, frequently occurred during the early postoperative period. At the last ex-

TABLE 5.—*Average, Minimum and Maximum Duration and Amplitude of the P Wave, P-R Interval and QRS Duration in 73 Cases of Patent Ductus Arteriosus (A) before and (B) after Ligation of the Ductus. The Measurements Were Derived from Lead II*

	P Wave						P-R Interval, sec.			QRS Duration, sec.		
	Amplitude, mv.			Duration, sec.								
	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.
A	0.125	0.05	0.20	0.085	0.06	0.14	0.146	0.10	0.19	0.068	0.04	0.10
B	0.098	0.05	0.20	0.075	0.05	0.14	0.132	0.10	0.17	0.060	0.04	0.10

amination all the patients showed a normal sinus rhythm.

Prior to operation, the average heart rate was 100.6 beats per minute. Following ligation of the ductus, a slight decrease in the heart rate usually occurred; the average rate was 92.2 beats per minute at the last examination.

P Wave, P-R Interval and QRS Duration. Following surgery, a slight diminution in the amplitude of the P wave was recorded in 35 instances (table 5). A slight decrease in the duration of the P wave occurred in 45 instances. A slight decrease in P-R interval and in the QRS duration was found in 35 instances.

Q-T Interval. Figure 6 shows that the Q-T interval was within normal limits in 25 instances. The remaining cases exhibited a prolonged Q-T interval. Following ligation of the ductus, a decrease in the Q-T interval was recorded in 30 instances. At the last examination, the Q-T interval was normal in 52 instances.

Electrical Axis of the QRS Complex and Electrocardiographic Position of the Heart. In 54 cases, the QRS complexes showed a balanced axis. Left axis deviation, which ranged between −60 and +30 degrees, was present in 13 cases. Five patients revealed right axis deviation between +90 and +150 degrees. Extreme right axis deviation with negative main deflections in the standard leads was recorded in one case (fig. 10). For the entire group, the average electrical angle was 52.2 degrees. Following ligation of the ductus, a slight increase in the electrical angle occurred in 40 instances. At the last postoperative examination the average angle was 60 degrees.

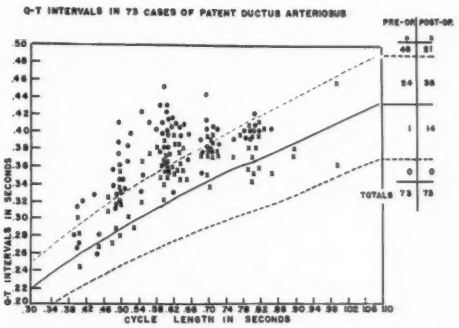


FIG. 6. The Q-T intervals were derived from Bazett's[20] formula Q-T = 0.404 $\sqrt{\text{R-R}}$. Prior to operation (o), in 48 instances, the Q-T interval was above the range of variation as described in healthy children.[21] Following ligation of the ductus, the Q-T interval decreased in 32 instances. In 52 cases the Q-T interval was within normal limits at the last examination.

At this time, 58 of the cases showed a balanced axis. Left and right axis deviation were present in respectively 11 and 4 cases.

The electrical position of the heart was vertical or semivertical in 60 cases. A horizontal or semihorizontal position was present in four cases. In seven instances, the position was intermediate. No significant changes occurred in the electrocardiographic position of the heart after the operation.

Q Wave. No significant changes were seen in the Q waves. In lead I, an isolated Q wave was present in 10 cases before and in 12 cases after the operation. Lead II and III showed a Q wave in respectively 34 and 44 cases. A slight increase in the amplitude of the Q wave was recorded in lead III; the average pre- and postoperative measurements were 0.178 and 0.205 mv. In leads V_1 and V_5, an isolated Q wave was recorded in 4 and in 68 cases, respectively; no changes occurred after operation.

R Wave. Following surgery, a decrease in the amplitude of the R wave in V_5 occurred in 66 cases (table 6). A slight decrease in the amplitude of the R wave usually occurred in the three standard leads and in aV_F. Figures 7 to 10 illustrate the postoperative changes in the R waves.

S Wave. In V_1, a significant decrease in the

TABLE 6.—*Average, Minimum and Maximum Amplitude of the R Wave in Millivolt in 73 Cases of Patent Ductus Arteriosus (A) before and (B) after Ligation of the Ductus. Leads Showing Significant Postoperative Changes in the R Wave Are Presented.*

	I			II			III			aV_F			V_5		
	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.	Av.	Min.	Max.
A	0.95	0.20	2.40	1.75	0.50	3.60	1.21	0	2.80	1.38	0.30	2.70	2.67	0.50	4.50
B	0.74	0.20	1.80	1.25	0.40	2.30	1.02	0	2.90	1.11	0.10	2.70	1.70	0.50	3.50

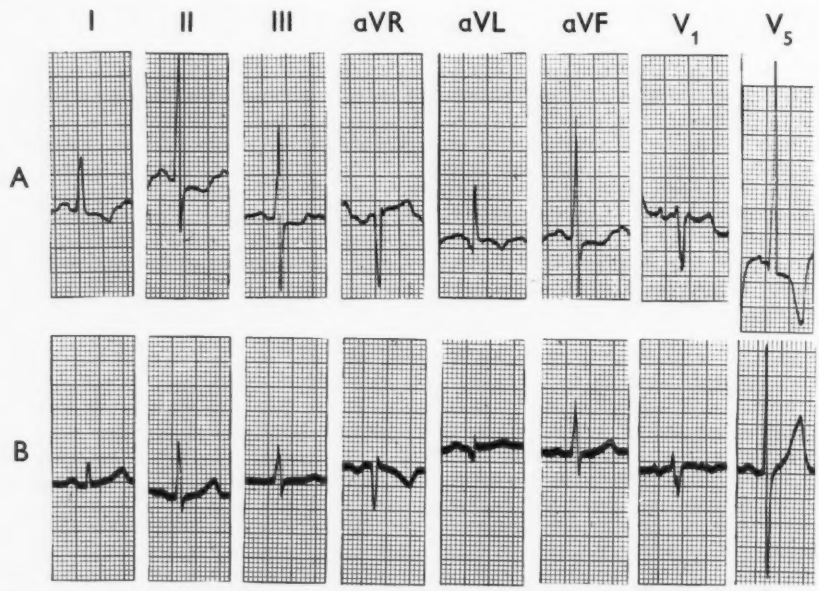


FIG. 7. *A*. Electrocardiogram of a girl, 7½ years of age, with patent ductus arteriosus. Depression of the S-T segments in leads I, II, III, aV_F and V_5. Negative or diphasic T waves in leads I, II, III, aV_L, aV_F and V_5. Delayed onset of the intrinsicoid deflection in V_5. The diameter of the ductus was 19 mm. *B*. Six months after ligation of the ductus. The S-T segments and the T waves have become normal. The amplitudes of the R waves have decreased in all the leads. Normal onset of the RS deflection in V_5.

amplitude of the S wave occurred in 55 instances; the average pre- and postoperative amplitudes were 1.58 and 1.04 mv. A corresponding increase in the amplitude of the S wave was registered in V_5. A slight decrease in the average amplitude of the S wave occurred in aV_R (from 1.13 to 0.89 mv.).

R/S and R/Q Ratio. A decrease in the R/S ratio in lead I and a corresponding increase in lead III were recorded in most of the cases. This was consistent with the slight postoperative shift of the electrical axis towards the right. In V_1, the R/S ratio was less than unity in 65 cases before and in 72 cases after operation. In V_5, the amplitude of the R wave exceeded that of the S wave in all the cases. Following ligation of the ductus, the R/S ratio in V_5 decreases in 53 instances. In aV_R, the amplitude of the R waves was greater than that of the main negative deflection in only four cases before and in three cases after operation. This lead showed a QS pattern in 39 cases (figs 7–9), an isolated Q wave in 21 cases (fig. 10) and an S wave in 13 instances. Following operation, a slight increase in the ratio between the positive and the negative

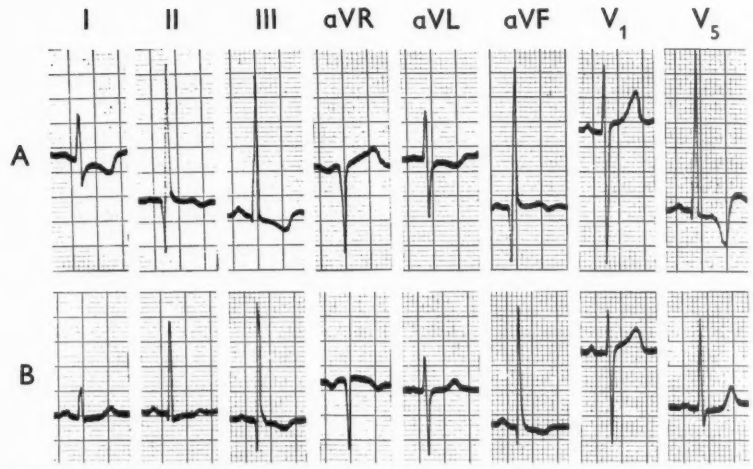


FIG. 8. *A*. Electrocardiogram of a girl, 9 years of age, with patent ductus arteriosus. Depression of the S-T segments in leads I, III and V_5. Negative or diphasic T waves in leads I, II, aV_L and V_5. Delayed onset of the intrinsicoid deflection in V_5. The diameter of the ductus was 12 mm. *B*. Eighteen months after ligation of the ductus. The S-T segments and the T waves have changed towards normal. The amplitude of the R waves has decreased particularly in V_5. Normal onset of the intrinsicoid deflection in V_5.

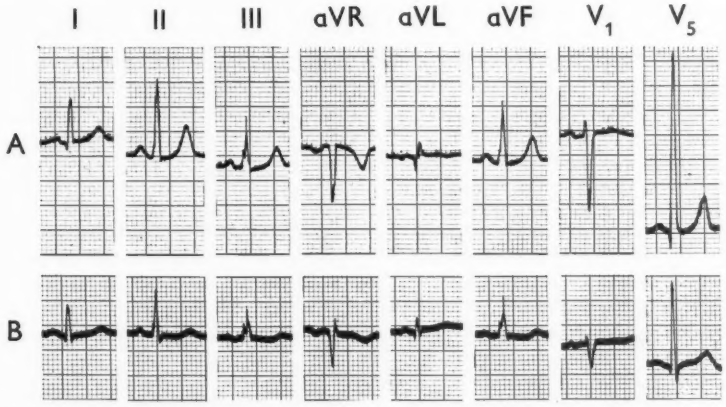


FIG. 9. *A*. Electrocardiogram of a woman, 25 years of age, with patent ductus arteriosus. The tracings are within normal limits except for the relatively high R wave and the slightly delayed onset of the intrinsicoid deflection in V_5. The diameter of the ductus was 5 mm. *B*. Fifteen months after ligation of the ductus. The voltage of the QRS complexes has decreased particularly in V_1 and V_5. Normal onset of the intrinsicoid deflection in V_5.

deflection in aV_R was recorded in 47 of the cases. Figures 7 to 10 illustrate the changes in the R/S ratios.

Onset of the Intrinsicoid Deflection. Prior to operation, V_5 showed an average time of onset of the intrinsicoid deflection of 0.038 second. Following surgery, a decrease in this measurement was recorded in 55 of the cases; the average measurement was 0.025 second at the last postoperative examination. No changes were seen in the time of onset of the intrinsicoid deflection in V_1 which was 0.022 second. An rSR′ or RSR′ pattern in V_1 suggestive of partial right bundle-branch block was re-

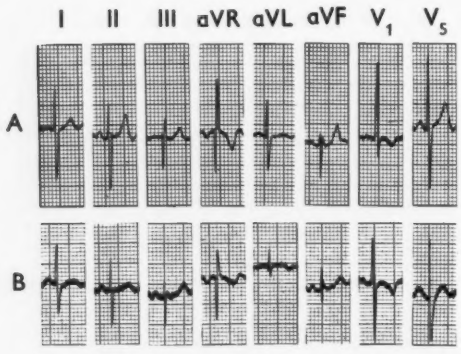


FIG. 10. *A*. Electrocardiogram of a male, 7 months of age, with patent ductus arteriosus. The infant was in cardiac failure. The electrocardiogram exhibits signs of right ventricular hypertrophy. Extreme right axis deviation. High R waves in aV_R and V_1. The diameter of the ductus was 8 mm. *B*. Eighteen months after ligation of the ductus. Left axis deviation. In aV_R and V_1, the ratios between the positive and the negative deflections of the QRS complex have decreased. The tracing is within normal limits.

TABLE 7.—*The S-T Segment in Different Leads in 73 Cases of Patent Ductus Arteriosus (A) before and (B) after Ligation of the Ductus*

	Normal S-T Segments in All Leads. No. of Cases	S-T Depression or Strain. No. of Cases							
		I	II	III	aV_R	aV_L	aV_F	V_1	V_5
A	48	13	8	3	1	4	10	—	17
B	66	2	3	1	1	—	2	1	2

corded in three cases before and in four cases after the operation (fig. 4).

S-T Segment. Prior to operation, 48 of the patients showed normal S-T segments in all the leads (table 7). The remainder of the patients revealed S-T depression or strain in one or more leads. These changes were most frequently recorded in leads V_5, I and aV_F. The S-T segments frequently became normal after the operation. At the last postoperative examination, the S-T segments were normal in all the leads in 66 instances. Figures 7 and 8 illustrate the postoperative changes in the S-T segments.

T Wave. Changes in the direction of the T waves were occasionally recorded (table 8). There was a slight postoperative increase in the average amplitude of the T wave in lead I. A slight decrease in this measurement was recorded in leads III, aV_F and V_5. Figures 7 to 10 illustrate the changes in the T waves.

Clinical Data

In 65 of the cases, a typical continuous murmur and electrocardiographic evidence of left ventricular preponderance was recorded. The remaining eight cases which presented atypical murmurs were confined to the youngest age groups. Prior to operation, seven of these patients showed electrocardiographic evidence of right ventricular or combined ventricular hypertrophy (fig. 10). Three of these patients showed signs of heart failure.

Prior to operation, the average systolic blood pressure was 108.3 mm. Hg, and no significant changes occurred. The diastolic pressure, on the other hand, increased in 62 cases; the average pre- and postoperative readings were 41.2 and 66.2 mm. Hg.

The size of the heart was within normal limits in 54 cases. Cardiac enlargement, with a cardiothoracic ratio between 45 and 60 per cent, was present in 14 instances. In five patients, all of whom were small children, the ratio exceeded 60 per cent. Following ligation of the ductus, a decrease in the size of the heart occurred in 16 cases. The most marked diminution in the size of the heart was usually seen in the youngest age groups. At the last postoperative examination, 10 patients revealed a moderate enlargement of the heart.

TABLE 8.—*The Direction of the T Wave in Different Leads in 73 Cases of Patent Ductus Arteriosus (A) before and (B) after Ligation of the Ductus*

Direction of the T Wave	I		II		III		aV_R		aV_L		aV_F		V_1		V_5	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Positive	64	72	70	70	63	54	4	2	40	45	71	70	12	11	67	71
Isoelectric or diphasic	3	—	—	3	6	12	1	—	13	13	1	1	8	7	—	—
Negative	6	1	3	—	4	7	68	71	20	15	1	2	53	55	6	2

No significant correlation was observed between the size of the heart and the degree of the electrocardiographic changes after the operation.

The diameter of the ductus varied between 5 and 19 mm. In 11 cases, the diameter exceeded 10 mm. There was as a rule a positive correlation between the size of the ductus and the changes in the electrocardiogram. Thus, the most marked changes were seen in patients with large ductuses, whereas the changes were less conspicuous in patients in whom the ductus was small (figs. 7 to 10).

Discussion

Coarctation of the aorta causes an increased load on the left side of the heart. Hence, in the present series, the changes in the electrocardiogram that occurred after surgical correction of the coarctation offered indirect evidence of the electrocardiographic pattern which occurs with left ventricular preponderance.

The electrocardiographic changes in coarctation were not, as a rule, as conspicuous as those seen in right-sided heart strain produced by pure pulmonary stenosis.[1] In many instances, the effect of the left ventricular strain on the electrocardiogram could be appreciated only by comparing the pre- and postoperative tracings.

Prior to operation, the average amplitude and duration of the P wave were within the normal limits as described in healthy young subjects.[43] Following surgery, a slight decrease in these measurements was recorded in about half of the cases. This decrease probably reflected a lessening of work required of the left auricle.

It is worthy of note that the Q-T interval was prolonged in the majority of cases of coarctation. This observation is in keeping with reports according to which a prolonged Q-T interval frequently occurs in adult patients with hypertensive heart disease.[44-48] As long ago as in 1892, Lüderitz[49] made an observation which is of considerable interest. In pulse tracings made on experimental animals, he registered a prolongation of the systole duration by compressing the aorta. It is, therefore, possible that the marked postoperative decrease in the Q-T intervals which was observed in the present series was not necessarily a sign of diminished cardiac hypertrophy but rather due to a shorting of the phase of contraction of the left ventricle.

Prior to operation, the electrocardiographic position of the heart was horizontal or semihorizontal in about one-fourth of the cases of coarctation. Yu and associates,[50] in an electrocardiographic study of 100 normal children, did not record a horizontal position in a single case, nor was this position observed in pure pulmonary stenosis.[1] Thus, a horizontal position of the heart in children seems to be suggestive of left ventricular preponderance. This assumption is supported by the fact that a shift of the electrical axis towards the right frequently occurred in coarctation after reduction of the work required of the left ventricle.

High voltage in the standard leads[51-53] and high R waves in V_5[53-56] have been considered electrocardiographic evidence of left ventricular hypertrophy. In the present series of coarctation the average amplitude of the R wave in the standard leads was at the upper limits of normal recorded for healthy children.[43] Following surgery, a decrease in the amplitude of the R wave was recorded in leads I, II, aV_L and in particular in V_5. Thus, the effect on the R waves of the diminution of the left ventricular load was best seen in these leads.

It is worthy of note that in aV_R the amplitude of the R wave was less than that of the main negative deflection in all the cases of coarctation. In pure pulmonary stenosis the R/S or R/Q ratio in aV_R was as a rule more than unity.[1] Thus, although an R/S or R/Q ratio in aV_R of less than unity is generally considered merely to indicate counterclockwise rotation of the heart,[51] it seems to offer indirect evidence of left ventricular preponderance.

According to Veasy and Adams,[32] the time of onset of the intrinsicoid deflection in V_5 in normal young subjects varies between 0.020 and 0.040 second. An increase in this measurement is considered by many authors a highly suggestive electrocardiographic sign of left ventricular hypertrophy.[32, 39, 51, 53, 54, 56] In the

present series of coarctation, the average ventricular activation time in V_5 was 0.035 second. Following surgery, a decrease in this measurement occurred in the majority of the cases; this suggested a lessening of the work required of the left ventricle. No corresponding changes were recorded in V_1 in which the average onset of the intrinsicoid deflection was normal before as well as after the operation. This suggests that the load on the right ventricle, contrary to that on the left ventricle, did not diminish after surgical correction of the coarctation.

Depression of the S-T segments and T-wave inversion in lead I[57-59] and in V_5[53-56] have been considered electrocardiographic signs of left ventricular hypertrophy and strain. In the present series of coarctation, S-T depression or strain was recorded in leads II and V_5 in about one quarter of the cases whereas the remaining leads rarely revealed such changes. Following surgery, the S-T segments usually became normal.

It is worthy of note that inversion of the T waves was never recorded in lead I and only exceptionally in leads II and V_5. Prior to operation, the average amplitude of the T wave in leads I, II, aV_F and V_5 was slightly less than the corresponding measurements in normal children.[43] On the whole, however, the results are in keeping with observations[32] according to which changes in the S-T segments and in the T waves are relatively rare in children with left ventricular hypertrophy in contrast to adult patients with hypertensive heart disease.

In the series of patent ductus arteriosus which presented a typical continuous murmur, the electrocardiograms showed a basic pattern similar to that recorded in coarctation. As a rule, however, the electrocardiographic changes indicating left ventricular preponderance were more conspicuous in patent ductus arteriosus than in coarctation. Insofar as the electrocardiographic signs of left ventricular strain diminished after ligation of the ductus, the same comments as outlined in coarctation apply to the majority of the cases of patent ductus arteriosus.

Seven of the patients with patent ductus arteriosus exhibited an electrocardiographic pattern indicative of right ventricular or combined ventricular hypertrophy. Cardiac catheterization, performed in four of these cases revealed an elevated pressure in the pulmonary artery. It has been suggested[38, 60] that pulmonary hypertension occuring in patients with patent ductus arteriosus may occasionally be due to changes in the pulmonary vascular bed. In the present series, the electrocardiographic signs of right ventricular hypertrophy markedly decreased after ligation of the ductus. Thus, it appears as if the increased load on the right ventricle in these seven cases was not primarily due to permanent structural changes in the pulmonary vascular bed.

Mannheimer and associates[61] have noticed that patients with patent ductus arteriosus frequently show a positive result of the hypoxia tolerance test. The electrocardiographic changes recorded during hypoxia were similar to those seen in coronary insufficiency. Following ligation of the ductus, the result of the test frequently became negative. This observation possibly suggests that the postoperative changes in the electrocardiogram which occurred in the present series may in part have been due to an improved coronary circulation.

The positive correlation which was found between the diameter of the ductus and the degree of the changes in the electrocardiogram is in keeping with observations made by Sokolow and Edgar.[13] Likewise, several authors have commented on the fact that the pulse pressure usually decreases after ligation of patent ductus arteriosus.[39, 62-64]

It is worthy of note that the size of the heart did not decrease in a substantial number of the cases after ligation of the ductus. This phenomenon has previously been observed by different authors.[29, 39] In the present series, the electrocardiogram usually revealed signs of a diminished load on the heart after ligation of the ductus. This observation, in conjunction with the corresponding observation made in pure pulmonary stenosis and in coarctation of the aorta, offers further evidence that electrocardiography is a sensitive means for measuring the degree of ventricular preponderance and, consequently, for the evaluation of the

benefits derived from surgical correction of cardiac defects.

Summary

Electrocardiograms of 41 cases of coarctation and of 73 cases of patent ductus arteriosus were analyzed before and after surgical correction of the defect. The majority of the patients were children. The time interval between the pre- and postoperative electrocardiograms varied between three months and five years.

Coarctation of the Aorta

Following surgery, a slight decrease in the heart rate occurred in the majority of the cases.

Prior to operation, the Q-T interval was prolonged in 35 of the cases. A decrease in the Q-T interval was recorded in 35 cases after the operation.

Twenty-five of the patients showed a balanced axis. Left axis deviation was present in 14 and right axis deviation in two instances. Postoperatively, a slight shift of the electrical axis towards the right occurred in the majority of the cases.

Following surgery, there was a slight decrease in the average amplitude of the R wave in leads I, II, aV_L and V_5.

In all the cases, the R/S ratio was less than unity in V_1 and greater than unity in V_5. Following surgery, there was as a rule an increase in the R/S ratio in V_1 and a corresponding decrease in the ratio in V_5.

The onset of the intrinsicoid deflection in V_5 was slightly delayed in the majority of the cases. Following surgery, this measurement usually decreased.

S-T depression or strain was recorded in leads II and V_5 in approximately one quarter of the cases. Following surgery, these changes disappeared in most of the cases.

The postoperative changes in the electrocardiogram were considered to be due to the diminished load on the left ventricle.

The size of the heart frequently remained unchanged even in cases which showed a marked postoperative drop in the blood pressure combined with electrocardiographic evidence of a diminished load on the left ventricle.

Patent Ductus Arteriosus

Prior to operation, three patients showed occasional extrasystoles. At the last postoperative examination, a normal sinus rhythm was recorded in all the cases. Following ligation of the ductus, there was a slight decrease in the average heart rate.

Sixty-five of the patients presented typical continuous murmurs. These patients revealed a basic electrocardiographic pattern similar to that in coarctation. The electrocardiographic changes indicative of left ventricular preponderance, however, were more conspicious in the cases of patent ductus arteriosus than in coarctation.

Seven of the patients showed electrocardiographic evidence of right ventricular or combined ventricular hypertrophy. All of these patients presented atypical murmurs.

Following ligation of the ductus, the electrocardiogram became normal in the majority of the cases. A positive correlation was found between the size of the ductus and the changes in the electrocardiogram.

The size of the heart frequently remained unchanged even in cases which showed electrocardiographic evidence of a diminished load on the heart.

Sumario Español

Los electrocardiogramas en 41 casos de coarctación y en 73 casos de conducto arterioso patente fueron analizados antes y después de correción quirúrgica del defecto. La mayoría de los pacientes fueron niños. El intervalo de tiempo entre los estudios electrocardiográficos pre y postoperatorios varió entre tres meses y cinco años.

Coarctación de la Aorta

Después de la operación ocurrió un ligero decremento en el pulso en la mayoría de los casos.

Antes de la operación, el intervalo Q-T estaba prolongado en 35 casos. Un decremento en el intervalo Q-T se registró en 35 casos luego de la operación.

Veinte y cinco de los pacientes mostraron un eje balanceado. Desviación de eje hacia la izquierda estuvo presente en 14 y desviación hacia la derecha en dos casos. Después de la operación un ligero cambio del eje eléctrico hacia la derecha ocurrió en la mayoría de los casos.

Después de la operación, hubo un ligero decremento en la amplitud promedio de la onda R en las derivaciones I, II, aV_L y V_5.

En V_1, la proporción R/S fué menos que unidad y en V_5 mayor que unidad en todos los casos. Después de la operación, por regla general ocurrió un incremento en la proporción de R/S en V_1 y un correspondiente decremento en la proporción en V_5.

El comienzo de la desviación intrinsecoide en V_5 estuvo ligeramente retardada en la mayoría de los casos. Luego de la operación, esta medida usualmente disminuyó.

Depresión del segmento S-T o esfuerzo fué registrado en las derivaciones II y V_5 en aproximadamente una cuarta parte de los casos. Después de la operación, estos cambios desaparecieron en la mayoría de los casos.

Los cambios postoperatorios en el electrocardiograma fueron considerados debidos a la disminución en trabajo del ventrículo izquierdo.

El tamaño del corazón frecuentemente permaneció inalterado aún en los casos que mostraron una caída marcada en la presión arterial acompañada de evidencia electrocardiográfica de disminución de esfuerzo del ventrículo izquierdo.

Conducto Arterioso patente.

Antes de la operación, tres pacientes mostraron extrasístoles ocasionales. En el último examen postoperatorio se registró un ritmo sinuatrial normal en todos los casos. Luego de la ligación del conducto hubo un ligero decremento en el pulso promedio. Sesenta y cinco pacientes presentaron soplos continuos típicos. Estos pacientes revelaron un patrón electrocardiográfico básico similar a aquel de la coarctación. Los cambios electrocardiográficos indicativos de preponderancia ventricular izquierda, sinembargo, fueron más conspicuous en los casos de conducto arterioso patente que en los de coarctación.

Siete de los pacientes mostraron evidencia electrocardiográficia de hipertrofiz ventricular derecha o de hipertrofia ventricular combinada. Todos estos pacientes presentaron soplos atípicos. Después de la ligación del conducto, el electrocardiograma se tornó a lo normal en la mayoría de los casos. Una correlación positiva se encontró entre el tamaño del conducto y los cambios en el electrocardiograma.

El tamaño del corazón frecuentemente permaneció inalterado aún en los casos que mostraron evidencia electrocardiográfica de disminución de esfuerzo en el corazón.

ACKNOWLEDGMENT

In gratitude for help and criticism obtained, these communications are dedicated to Dr. Helen B. Taussig, Physician-in-Charge of the Cardiac Clinic of the Harriet Lane Home.

REFERENCES

[1] LANDTMAN, B.: Postoperative changes in the electrocardiogram in congenital heart disease. I. Pure pulmonary stenosis. Circulation **10:** 859, 1954.

[2] CAMPBELL, M., AND SUZMAN, S. S.: Coarctation of the aorta. Brit. Heart J. **4:** 185, 1947.

[3] CHRISTENSEN, N. A., AND HINES, E. A., JR.: Clinical features in coarctation of the aorta. A review of 96 cases. Proc. Staff Meet., Mayo Clin. **23:** 339, 1948.

[4] GROSS, R. E.: Coarctation of the aorta. Circulation **7:** 757, 1953.

[5] KING, J. T., JR.: Stenosis of the isthmus (coarctation) of the aorta and its diagnosis during life. Arch. Int. Med. **38:** 69, 1926.

[6] NEWMAN, M.: Coarctation of the aorta. Review of twenty-three cases. Brit. Heart J. **10:** 50, 1948.

[7] ABBOTT, M.: Coarctation of the aorta of the adult type. II. A statistical study and historical retrospect of two hundred recorded cases, with autopsy, of stenosis or obliteration of the descending arch in subjects above the age of two years. Am. Heart J. **3:** 574, 1928.

[8] LEWIS, T.: Material relating to coarctation of the aorta of the adult type. Heart **16:** 205, 1933.

[9] SCHNITKER, M. A.: The Electrocardiogram in Congenital Heart Disease. Cambridge, Mass., Harvard University Press, 1940.

[10] STEWART, H. J., HASKELL, H. S., AND EVANS, W. F.: The peripheral blood flow and other observations in coarctation of the aorta. Am. Heart J. **28:** 217, 1944.

[11] TAUSSIG, H. B.: Congenital Malformations of the Heart. New York, Commonwealth Fund, 1947.

[12] RHODES, P. H., AND DURBIN, E.: Coarctation of

the aorta in childhood. Am. J. Dis. Child. **64:** 1073, 1942.

[13] Sokolow, M., and Edgar, A. L.: A study of the V leads in congenital heart disease. Am. Heart J. **40:** 232, 1950.

[14] Oglesby, P., Myers, G. S., and Campbell, J. A.: The electrocardiogram in congenital heart disease. Circulation **3:** 564, 1951.

[15] Alimurung, M. M., and Smith, R. M.: Electrocardiographic studies during operation for coarctation of the aorta. Brit. Heart J. **13:** 303, 1951.

[16] Clagett, O. T., and Jampolis, R. W.: Coarctation of the aorta. A study of seventy cases in which surgical exploration was performed. Arch. Surg. **63:** 337, 1951.

[17] Stalker, H.: Coarctation of the aorta; a case with right axis deviation of the electrocardiogram and auricular fibrillation with some statistics. J. Michigan M. Soc. **41:** 40, 1942.

[18] Olney, M. B., and Stephens, H. B.: Coarctation of the aorta in children. Observations in fourteen cases. J. Pediat. **37:** 639, 1950.

[19] Weissel, W.: Unipolare Electrocardiographie kongenitaler Anomalien des Herzen. Cardiologia **16:** 191, 1950.

[20] Bazett, H. C.: An analysis of the time-relations of electrocardiograms. Heart **7:** 354, 1920.

[21] Alimurung, M. M., Joseph, L. G., Craige, E., and Massell, B. F.: The Q-T interval in normal infants and children. Circulation **1:** 1329, 1950.

[22] Benn, J.: The prognosis of patent ductus arteriosus. Brit. Heart J. **9:** 283, 1947.

[23] East, T.: Ligation of the patent ductus arteriosus. Brit. Heart J. **7:** 95, 1945.

[24] Gilchrist, A. R.: Patent ductus arteriosus and its surgical treatment. Brit. Heart J. **7:** 1, 1945.

[25] Gross, R. E., and Longino, L. A.: The patent ductus arteriosus. Observations from 412 surgically treated cases. Circulation **3:** 125, 1951.

[26] Hertzman, V. O., and Strong, G. F.: Patent ductus arteriosus. Canad. M. A. J. **61:** 495, 1949.

[27] Shapiro, M. J.: The preoperative diagnosis of patent ductus arteriosus. J. A. M. A. **126:** 934, 1944.

[28] Cabrera, E., Borges, S., and Novelo, S.: Estudio electrocardiografico de la persistencia del conducto arterioso. Arch. Inst. cardiol. Mexico **20:** 426, 1950.

[29] Ekström, G.: The surgical treatment of patent ductus arteriosus. Acta chirurg. scandinav. Suppl. 169, 1952.

[30] Mannheimer, E.: Nouveaux points de vue sur l'etablissement de la persistence du canal artériel. Arch. mal. coeur **43:** 324, 1950.

[31] Robles, C., and Benavides, P.: Consideraciones averca del tratimento quirurgico de la persistencia del conducto arterioso. Arch. Inst cardiol. Mexico **19:** 1, 1949.

[32] Veasy, G., and Adams, F. H.: Unipolar lead electrocardiography in children. Pediatrics **9:** 395, 1952.

[33] Taussig, H. B.: Diagnosis and management of common malformations of the heart. Circulation **6:** 6, 1952.

[34] Ziegler, R. F.: The importance of patent ductus arteriosus in infants. Am. Heart J. **43:** 553, 1952.

[35] Vesell, H., and Kross, I.: Patent ductus arteriosus with subacute endocarditis. Arch. Int. Med. **77:** 659, 1946.

[36] Gross, R. E.: The patent ductus arteriosus. Am. J. Med. **12:** 472, 1952.

[37] Dammann, J. F., Jr., and Sell, C. G. R.: Patent ductus arteriosus in the absence of a continuous murmur. Circulation **6:** 110, 1952.

[38] Hultgren, H., Selzer, A., Purdy, A., Holman, E., and Gerbode, F.: The syndrome of patent ductus arteriosus with pulmonary hypertension. Circulation **8:** 15, 1953.

[39] Taussig, H. B.: Personal communication.

[40] Cabrera, E., de Maura Campos, C., and Caminero, J. F.: La persistencia del conducto arterioso desde un punto de vista electrocardiografico. Arch. Inst. cardiol. Mexico **22:** 151, 1952.

[41] Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in congenital heart disease. Am. J. Roentgenol. **50:** 306, 1943.

[42] Blalock, A.: Operative closure of the patent ductus arteriosus. Surg. Gynec. & Obst. **82:** 113, 1946.

[43] Ziegler, R. F.: Electrocardiographic studies in normal infants and children. Springfield, Ill., Charles C Thomas, 1951.

[44] Alexander, J. K., Ferrer, M. I., Harvey, R. M., and Cournand, A.: The Q-T interval in chronic cor pulmonale. Circulation **3:** 733, 1951.

[45] Hegglin, R., and Holzmann, M.: Die klinische Bedeutung des verlängten QT-Distanz (Systoledauer) in Elektrokardiogramm. Ztschr. klin. Med. **132:** 1, 1937.

[46] Holldack, K., Weygand, A., Kuhn, E., and Ehrenpreis, W.: Die relative Systoledauer in bezug zur QT-Zeit bei Herzfehlern. Ztschr. Kreislaufforsch. **42:** 415, 1953.

[47] Phang, S. H., and White, P. D.: The duration of ventricular systole as measured by the Q-T interval of the electrocardiogram, with especial reference to cardiac enlargement with and without congestive failure. Am. Heart J. **26:** 108, 1943.

[48] Smělý, R. F.: QT beim Normalen und bei einigen Krankheiten. Cardiologia **9:** 231, 1945.

[49] Lüderitz, C.: Versuche über den Ablauf des

Blutdruckes bei Aortenstenose. Ztschr. klin. Med. **20:** 374, 1892.

[50] Yu, P. N. G., Joos, H. A., and Katsampes, C. P.: Unipolar electrocardiogram in normal infants and children. Am. Heart J. **41:** 91, 1951.

[51] Goldberger, E.: Unipolar lead electrocardiography. Philadelphia, Lea & Febiger, 1949.

[52] Gubner, R. S., and Ungerleider, H. E.: Electrocardiographic criteria of left ventricular hypertrophy. Arch. Int. Med. **72:** 196, 1943.

[53] Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., de Oliviera, R., and Barker, P. S.: The precordial electrocardiogram. Am. Heart J. **27:** 19, 1944.

[54] Pagnoni, A., and Goodwin, H. J. F.: The cardiographic diagnosis of combined ventricular hypertrophy. Brit. Heart J. **14:** 451, 1952.

[55] Wood, P.: Congenital heart disease. Brit. M. J. **2:** 639, 1950.

[56] Sokolow, M., and Lyon, T. P.: The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am. Heart J. **37:** 161, 1949.

[57] Herrmann, G. R., and Wilson, F. N.: Ventricular hypertrophy. A comparison of electrocardiographic and post mortem observations. Heart **9:** 91, 1922.

[58] Kaplan, L. G., and Katz, L. N.: The characteristic electrocardiogram in left ventricular strain with and without axis deviation. Am. J. M. Sc. **201:** 676, 1941.

[59] Willius, F. A.: Electrocardiography and prognosis. Arch. Int. Med. **30:** 434, 1922.

[60] Chapman, C., and Robbins, S.: Patent ductus arteriosus with pulmonary vascular sclerosis and cyanosis. Ann. Int. Med. **21:** 312, 1944.

[61] Mannheimer, E., Carlgren, L. E., and Graf, W.: Further experience with the hypoxia tolerance test in children. J. Pediat. **33:** 58, 1948.

[62] Cassels, D. E., Morse, M., and Adams, W. E.: Effect of the patent ductus arteriosus on the pulmonary flow, blood volume, heart rate, blood pressure, arterial blood gases and pH. Pediatrics **6:** 557, 1950.

[63] Lewes, D.: Exercise test in patent ductus arteriosus. Brit. Heart J. **14:** 357, 1952.

[64] Taylor, B. E., Pollack, A. A., Burchell, H. B., Clagett, O. T., and Wood, E. H.: Studies on the pulmonary and systemic arterial pressure in cases of patent ductus arteriosus with special reference to effect of surgical closure. J. Clin. Investigation **29:** 745, 1950.

Studies on Tolerance to Ganglionic Blocking Agents in Man

Reversal of Depressor Action of Quaternary Ammonium Compounds

By A. S. Dontas, M.D., and S. W. Hoobler, M.D.

The hypotensive effects of intravenous injections of tetraethylammonium and hexamethonium chloride diminish and finally become pressor during the course of short-term treatment with subcutaneous hexamethonium. Evidence is presented to indicate that this "tolerance" is associated with a decreased sympathetic tone in the feet and forearm and is not due to increased amounts of circulating adrenal medullary or cortical hormones. Possibilities are discussed for this apparent vascular autonomy and the locus of vasoconstriction. Cross tolerance appeared between several ganglionic blocking agents tested and extended to a minor degree to adrenergic blocking agents.

ONE of the main disadvantages of ganglionic blocking agents in the treatment of hypertension is the development of "tolerance." The present study seeks to identify the mechanisms and vascular areas involved in this phenomenon and also in the development of cross tolerance between several different ganglionic blocking agents.

Method

Twelve patients, with moderate to severe essential hypertension, were studied in the Cardiovascular Unit of the University of Michigan Hospital for a period of 10 to 15 days, prior to, during and after a short period of treatment with parenteral hexamethonium. Of the twelve, three (A.P.,* H.T., J.P.) had been submitted to bilateral supradiaphragmatic splanchnicectomy, three months to six years previously, and one (E.B.) had a dorsolumbar sympathectomy five years previously and an additional extension of the original operation 12 months before the study. Their renal status was variable, but at the time of the study, only two (L.G.* and M.P.) had elevated serum creatinine or nonprotein nitrogen levels, while the others were definitely within normal limits. The patients were kept on a low sodium diet and remained ambulatory in the ward during their treatment with hexamethonium. The daily dose was usually constant for each patient for the period of observation and varied between 30 and 100 mg. per day, given subcutaneously in four equal doses every six hours. In six of the patients, *foot and forearm blood flows* were measured by venous occlusion plethysmography in a temperature-controlled room (70 to 74 F.) with a collecting cuff pressure of 80 mm. Hg. In no case did collecting pressure exceed diastolic pressure. After the subject had rested, three series of blood flow determinations at five-minute intervals were performed, each series consisting of five observations made at 20-second intervals. After drug injections, blood flows were determined in successive series of five observations every 20 seconds until a maximum had been reached. The average of three control series was designated as the "resting" blood flow and of five consecutive determinations at the time of maximum increase as average "maximum" blood flow for the respective area.

The effects of intravenous injections of 50 to 300 mg. of tetraethylammonium chloride (TEAC) and 7 to 30 mg. hexamethonium chloride (C-6) given about 45 minutes later were studied at frequent intervals before, during and for one or two days after the treatment. The injections were given two to four hours after the therapeutic subcutaneous hexamethonium injection on the ward.

Results

A. *Effects on Blood Pressure*

Injection of tetraethylammonium chloride in all our patients *prior* to therapy by hexa-

From the Department of Internal Medicine, University of Michigan, Ann Arbor, Mich.

Supported by research grants from the National Heart Institute, National Institutes of Health, and by the Michigan Heart Association.

* Patients A.P. and L.G. were studied only for their blood pressure changes and are not included in the tables in which blood flow and/or other special studies are recorded.

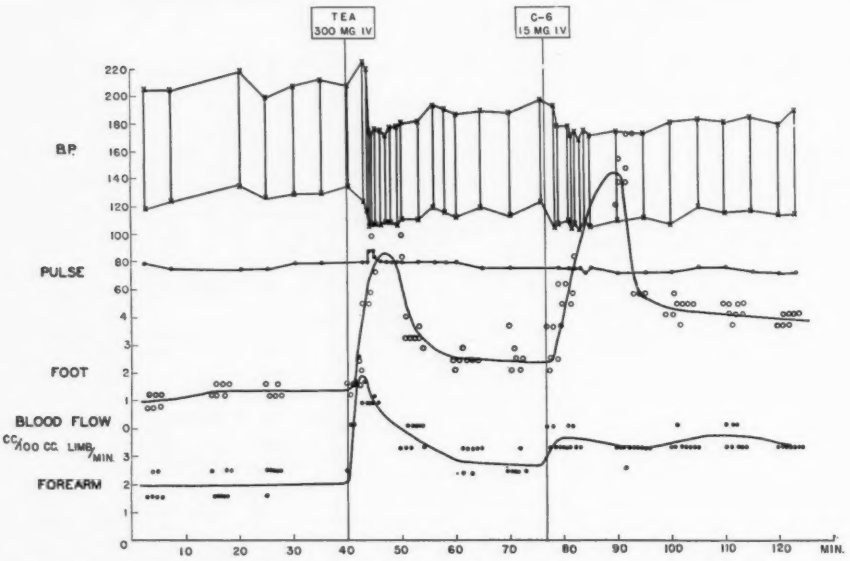


FIG. 1. Hemodynamic effects of intravenous injections of tetraethylammonium chloride and hexamethonium in the pretolerant state. For details see text.

methonium (see fig. 1) had the following effects: (1) A rapid initial rise in blood pressure, mainly systolic, developed. This lasted about 30 seconds and was associated with the well-known disagreeable tingling sensations. At the same time, the heart rate usually showed a slight increase. The peripheral vasodilatation, as measured by plethysmography, was already obvious at this stage. (2) A subsequent hypotensive response to tetraethylammonium chloride occurred. This was usually accompanied by subsidence of the initial disagreeable feelings and only a sensation of "cold" over the entire body persisted somewhat longer. The heart rate at this stage had returned to or slightly below the preinjection levels, although in occasional patients showing marked blood pressure drops there was a moderate tachycardia, as evidence of the incomplete blockade of the cardiac ganglia. Peripheral vasodilatation reached its peak during this stage, the foot and forearm resistance being reduced to one-third to one-fifth of the original values. (3) A phase during which blood pressure returned to the control levels, and the peripheral vasodilatation receded partially, lasted from 20 to 30 minutes. It was apparent that blood pressure-compensating mechanisms preceded the recovery of vasoconstrictor tone in the foot and forearm.

The main differences between the actions of tetraethylammonium chloride and those of the other ganglionic blocking agents tested (hexamethonium, pendiomide, and the trivalent ganglionic blocking agent SU-1194*) were the following: The initial blood pressure rise was missing, as were the sensations of cold and prickling with these latter drugs, and an agreeable feeling of general warmth was noted. The heart rate remained the same or decreased (especially with SU-1194), even during the initial sharp drop in blood pressure; the hypotension and peripheral vasodilatation were longer lasting and some differences in the loci of maximal response were occasionally observed. Figure 1 shows the difference in the forearm responses to tetraethylammonium chloride and hexamethonium, in a case where the foot increases were qualitatively similar.

When the injections of tetraethylammonium chloride were repeated on consecutive days

* We would like to express our thanks to Dr. F. F. Yonkman, Ciba Pharmaceutical Products, Inc., for the supply of this agent.

after therapy with hexamethonium had started, the following changes were observed: The initial rise remained the same, but the transition toward the hypotensive phase became less and less abrupt. Simultaneously, the maximum blood pressure drop became less and its duration shorter. In 11 of the 12 patients studied, a point was eventually reached where no blood pressure drop after the tetraethylammonium chloride injection occurred, while the initial rise now lasted occasionally as long as 10 minutes. The subjective feelings in response to the injection of tetraethylammonium chloride were never altered. We defined as "complete tolerance" the period when the hypotensive response in the *supine* position was entirely missing. Resting recumbent blood pressures, as can be seen from tables 1 and 2, usually fell somewhat during treatment with hexamethonium and then gradually rose as "tolerance" developed. The mean control blood pressure of our six patients studied by plethysmography was 171.6 ± 6.2 and had dropped to 154 ± 5.7 at the time of tetraethylammonium chloride reversals; the pressor responses to tetraethylammonium chloride and hexamethonium did not seem to bear any relation to the resting supine blood pressures, occurring at lower as well as occasionally at higher than the pretreatment levels. During this entire period, cold pressor responses were only moderately depressed, as further evidence of partial ganglionic blockade.

The other drugs were tested more rarely, usually not more than once or twice weekly. Hexamethonium given intravenously at the height of "tolerance" also exerted pressor effects in the majority of cases, while in the rest it was devoid of any depressor action. However, the rise occurred slowly and the decline also was delayed, occasionally lasting up to 30 minutes. In one instance, up to 60 mg. of hexamethonium given in infusion did not overcome the slow blood pressure rise. Pendiomide (30 mg.) also caused a reversal to a pressor response occurring simultaneously with the reversal to tetraethylammonium chloride. The onset and offset of effect were rapid, resembling those observed after tetraethylammonium chloride. The tertiary ganglionic blocking agent SU-1194 showed a considerable difference in the two patients tested. Refractoriness to its depressor action appeared much later than that to tetraethylammonium chloride, responses to it being quantitatively equal at a time when the "TEA-floor" had risen considerably. However, after complete "tolerance" to tetraethylammonium chloride had been reached for some days, the depressor action of SU-1194 gradually lessened, and one patient became completely tolerant to it (table 3). In our limited experience with this agent, we have not seen pressor responses following its injection.

B. *Effects on Blood Flow*

As mentioned above, in six of our patients we studied the changes in peripheral blood flow through a muscular (forearm) and a less muscular (foot) area after injection of the same amounts of tetraethylammonium chloride and hexamethonium chloride before, during and after the period of development of tolerance. The resting blood flows of both foot and forearm did not present definite changes compared with those obtained during the pretreatment test (fig. 2). It is obvious, therefore, when the drug is given every six hours subcutaneously, that repeated vasodilatations such as are demonstrated in figure 1 do not persist, at least with the small doses used in this study. In the majority of our cases the large drop in foot resistance following the injection of tetraethylammonium chloride observed before treatment, is lessened after tolerance has developed; the mean drop in foot resistance being 56.5 per cent before and 38.3 per cent during tolerance (table 1). The mean forearm resistance, though showing more scatter, is also converted from a 36.4 per cent drop to a 2.8 per cent rise during tolerance, which difference is close to statistical significance ($p = 0.06$). It must be stressed that the lessened decreases in resistance are largely a result of the failure to produce a drop in blood pressure during "tolerance," while increases in blood flow still occurred, although to a somewhat lesser degree. Similar changes were observed in the response of foot and forearm circulations to intravenous hexamethonium administration (table 2). The lessened drop of foot resistance (−59.0 per

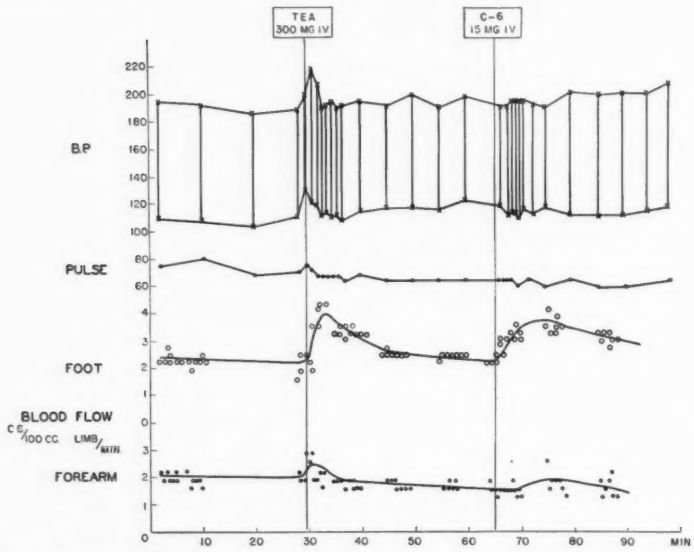


FIG. 2. Hemodynamic effects of intravenous injection of tetraethylammonium chloride and hexamethonium during tolerance to hexamethonium. Patient is the same as in figure 1, after five days of treatment with hexamethonium.

TABLE 1.—*Responses of Blood Pressure and Extremital Circulation to Intravenous Tetraethylammonium Chloride before, during and after Tolerance to Ganglionic Blockade by Hexamethonium*

	Test Dose mg.	Mean Blood Pressure			% Change in Mean Blood Pressure			% Change in Foot Resistance			% Change in Forearm Resistance		
		Before	During	After	Before	During	After	Before	During	After	Before	During	After
M. P.	300	168.5	150.0	155.7	−15.4	+10.7	−14.3	−83.0	−19.3	−84.4	−80.0	−7.7	—
C. C.	300	165.5	154.0	188.5	−9.4	+13.0	−9.3	−59.6	−33.3	−51.0	−51.0	−24.7	−36.3
M. V.	300	178.0	178.0	160.5	−10.4	+3.7	−2.5	−55.2	−46.6	−51.2	—	—	—
H. T.	300	169.5	141.5	149.0	−26.8	−4.9	−3.4	−84.3	−84.7	−76.4	−42.2	+36.7	−28.3
E. B.	300	197.0	141.5	201.0	−13.2	+23.3	−5.5	−11.6	+3.5	−21.3	−9.4	+17.0	−32.5
J. P.	250	151.0	162.0	167.0	−6.0	+8.6	0.0	−45.8	−49.4	−68.3	+0.8	−7.6	−23.5
Mean		171.6	154.5	170.1	−13.5	+7.4	−5.8	−56.5	−38.3	−58.8	−36.4	+2.8	−30.1
S.E.		±6.3	±5.7	±8.2	±3.0	±4.0	±2.1	±10.9	±12.2	±9.3	±46.0	±10.8	±2.7
		p = 0.11			p = 0.001			p = 0.14			p = 0.06		

S.E., standard error of the mean.

Mean blood pressure is calculated as $\frac{\text{systolic} + \text{diastolic}}{2}$.

Resistance calculated as $\frac{\text{mean blood pressure}}{\text{blood flow in ml./100 ml. of limb vol./min}}$.

cent to −21.8 per cent respectively) and especially the clear conversion to vasoconstriction in the forearm (from a mean of −53.4 per cent to +23.8 per cent, which is statistically significant) are also obvious. An interesting comparison is that between the blood pressure changes induced by these drugs and the resistance changes of the regional circulations studied. Although the mean hypotensive responses to both tetraethylammonium chloride and hexamethonium were approximately equal the drop in forearm resistance induced by tetraethylammonium chloride in the pre-"tolerant" stage was much less than that in-

TABLE 2.—*Responses of Blood Pressure and Extremital Circulation to Intravenous Hexamethonium before, during and after Tolerance to Ganglionic Blockade by Hexamethonium*

	Test Dose mg.	Mean Resting Blood Pressure			% Change in Mean Blood Pressure			% Change in Foot Resistance			% Change in Forearm Resistance		
		Before	During	After	Before	During	After	Before	During	After	Before	During	After
M. P.	15	168.5	150.0	—	−15.7	+3.3	—	−88.4	−32.0	—	−66.8	+14.8	—
C. C.	15	165.5	154.0	183.0	−16.7	+7.5	−11.5	−67.2	−1.0	−26.2	−60.0	+12.6	−21.7
M. V.	36	160.0	178.0	165.0	−10.6	+5.9	−4.2	−46.0	−34.3	−45.3	—	—	—
H. T.	15	166.0	141.5	143.5	−15.7	+6.0	−10.5	−62.5	−71.0	−86.2	−55.5	+35.4	−45.6
E. B.	15	183.0	141.5	182.0	−18.9	+21.9	−6.5	−31.0	−4.2	+3.6	−31.0	+36.7	−18.0
J. P.	7.5	—	168.0	172.0	—	+6.6	−1.2	—	+11.7	−18.4	—	+19.4	−15.4
Mean		168.5	155.5	169.1	−15.5	+8.5	−6.8	−59.0	−21.8	−35.9	−53.4	+23.8	−25.2
S.E.		±3.8	±6.0	±6.4	±1.4	±2.7	±1.9	±9.7	±12.2	±14.2	±7.8	±5.1	±6.9
		p = 0.19			p = 0.01			p = 0.09			p = 0.01		

duced by hexamethonium. On the other hand, the conversion of the initial forearm vasodilatation to a constriction occurred more uniformly with hexamethonium than with tetraethylammonium chloride.

The marked initial reduction of foot resistance with both substances still occurred with tetraethylammonium chloride during "tolerance," while the hexamethonium effect was much weaker.

C. *Studies Concerning the Mechanism of Tolerance*

I. *Adrenergic Factors.* It has been shown that strong doses of tetraethylammonium chloride may release epinephrine from the adrenals by direct stimulation, and this property has been used as a diagnostic test in pheochromocytoma.[1] We therefore investigated the possibility that, in our patients, rising amounts of circulating adrenergic substances might not only be responsible for maintaining the basal resting blood pressure during tolerance, but their acute release might explain the blood pressure rises occurring after tetraethylammonium chloride and hexamethonium, given intravenously in the "tolerant" state.

The areas of vasoconstriction, however, are different. In figure 3, obtained from patient E.B. during tolerance to hexamethonium, the blood pressure rise following 5 micrograms of norepinephrine equals that of 300 mg. of tetraethylammonium chloride. Norepinephrine, however, acts almost entirely on the foot circulation while tetraethylammonium chloride does not change appreciably the flow in either foot or forearm. The reflex bradycardia with norepinephrine is also missing with tetraethylammonium chloride. Repeated experiments on two of our patients (M.P. and J.P.) with the adrenergic blocking agent Dibenzyline brought further evidence that *epinephrine* is very probably not the cause of the recurrent hypertension during tolerance, since both patients did not show the sharp decline in blood pressure

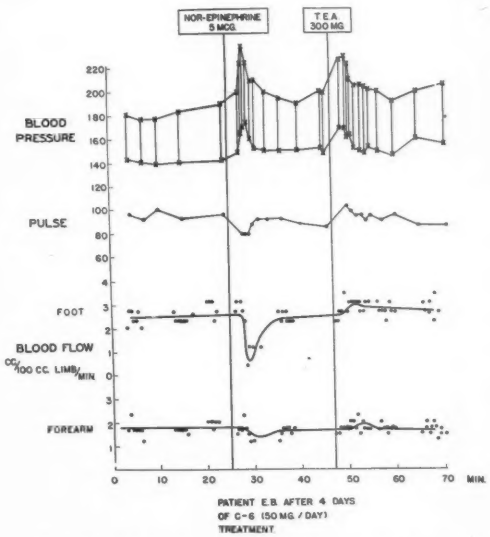


FIG. 3. Comparison of hemodynamic changes of equipressor doses of tetraethylammonium chloride and norepinephrine; tolerant patient.

TABLE 3.—*Hypotensive Action of Drugs before and after Development of "Tolerance" to Hexamethonium*

Patient	Drug	Blood Pressure (mm. Hg)		Max. Response to Drug (mm. Hg)		Max. Change after TEA	
		Before "Tolerance"	After "Tolerance"	Before	After	Before	After
M. P.	Dibenzyline 1 mg./Kg. i.v.	198/114	193/107	−18/−8	0/+6	−30/−18	+21/+13
J. P.	Dibenzyline 1 mg./Kg. i.v.	193/120	180/124	−13/−22	+10/+4	−58/−38	−12/−2
G. F.	Regitine 10 mg. i.v.	185/120	182/118	−12/−14	−8/−4	−42/−17	0/+3
E. B.	Regitine 5 mg. i.v.	198/140	205/150	−8/−16	−9/−12	−44/−21	+24/+15
G. F.	SU 1194 250 mg. i.v.	196/134	190/114	−39/−24	−24/−10	−46/−16	−5/0
S. C.	SU 1194 150 mg. i.v.	240/120	204/115	−70/−8	0/−3	−82/−10	0/+2
S. C.	Histamine 0.025 mg. i.v.	202/122	212/122	−54/−22	−84/−44	−24/−16	0/+2
G. F.	Protoveratrine 0.1 mg. i.v.	200/126	188/120	−55/−35	−44/−24	−48/−17	−22/−4

Before-"Tolerance" blood pressures represent the usual readings. Responses to tetraethylammonium chloride before and after "tolerance" refer to the test performed nearest to the time of administration of the drug in question and usually within 12 hours. Dose of tetraethylammonium chloride given intravenously was variable but the same for any one patient.

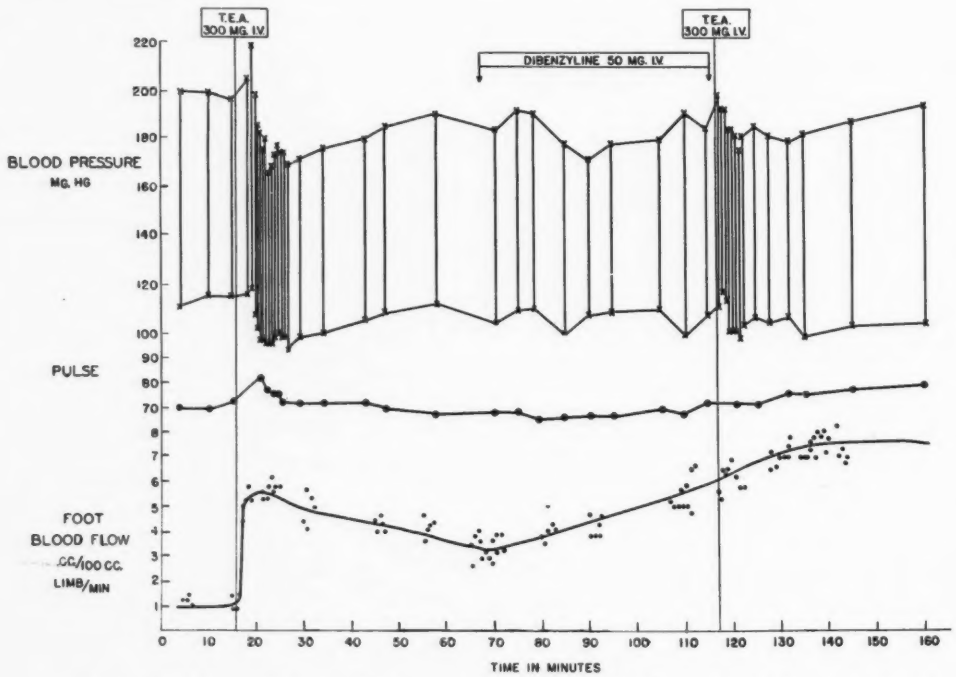


FIG. 4. Nontolerant patient. Hemodynamic effects of tetraethylammonium chloride before and after Dibenzyline infusion.

usually associated with this drug when hypertension is due to adrenergic substances (table 3). Moreover, the acute rise in pressure after tetraethylammonium chloride is also not due to epinephrine release, since it cannot be prevented by prior infusion with Dibenzyline (fig. 4). Similar results were obtained with the less specific adrenergic blocking agent, Regitine, an imidazoline derivative, tried repeatedly in two other patients (table 3). With this agent, the blood pressure decreases following tolerance were considerably reduced more or less in parallel with reductions in the response to tetraethylammonium chloride. These experiments suggest that epinephrine is not present in increased amounts in the blood in the tolerant state.

II. *Vascular Reactivity.* Direct vasodilators, such as histamine, were still active during the refractory state, indicating that reactivity of the vascular wall is not diminished during tolerance (table 3).

III. *Adrenocortical Mechanisms.* Although direct measurements of the output of 17-ketosteroids were not done, three of our patients, who became completely or partially tolerant to hexamethonium treatment, showed either no decrease or a mild rise in total circulating eosinophils during their treatment; body weight of our patients also showed a downward trend, as they were on a low sodium diet.

Discussion

I. *Explanation of the Conversion of the Acute Depressor Effect of Tetraethylammonium Chloride to a Pressor One*

The pressor action of tetraethylammonium chloride has been ascribed to adrenaline release,[2, 3] but its persistence in our experiments after Dibenzyline makes this explanation unlikely.

Another possibility would be the activation of pressor pathways not blocked by tetraethylammonium chloride, such as the ones described by Freyburger and co-workers in the dog.[4] The afferent limb of this reflex arc might rise from aortic and carotid chemoreceptors which can be stimulated by tetraethylammonium chloride and hexamethonium under partial blockade.[5] Such chemoreceptor stimulation would then increase blood pressure through channels which might not be vulnerable to ganglionic blocking agents.

A final possibility, which we favor, is that tetraethylammonium chloride is directly vasoconstrictor, in the concentration momentarily reached following an initial injection. A number of authors have reported acute vasoconstrictor effects of tetraethylammonium chloride on local vascular beds.[6, 7, 8] We believe that when sympathetic vasomotor tone is inhibited, the vasodilator and depressor component of the action of tetraethylammonium chloride is absent, while the vasoconstrictor effect remains and hence the blood pressure rises. If sympathetic tone is suppressed, the drug becomes pressor as after multiple injections in the dog,[6] after corticotropin (ACTH) administration,[9] and after total sympathectomy in man.[10] Such an action would explain the initial blood pressure rises that frequently precede the depressor phase when tetraethylammonium chloride is rapidly injected intravenously. The pressor effect of hexamethonium in our experiments may possibly have the same explanation, although it is said not to have a local vasoconstrictor action in animals.[11] The irregularity and delay in appearance of pressor effects in the tolerant state makes this clinical observation less certain than those involving tetraethylammonium chloride. We believe that the vasoconstrictor effects are not the indirect result of ganglionic blockade (e.g. differential blockade of vasodilators) in a tolerant patient, but are more likely a side effect peculiar to tetraethylammonium chloride itself, like paresthesias and other signs of excitation of peripheral structures which do not occur with other acutely acting ganglioplegic drugs.

II. *Explanation of the Mechanism of "Tolerance" to Hexamethonium*

It seems certain that establishment of "tolerance" to ganglionic blocking agents is not, as in the case of many other drugs, due to increased efficiency of inactivation, since they are not destroyed or inactivated in the body. Renal excretion is probably not intensified.

Furthermore, during hexamethonium treatment, "tolerance" to parasympathetic blocking effects on the pupil, gut or salivary secretion does not appear, according to the observations of Morrison.[12] The development of "tolerance" to adrenergic blocking drugs has also been reported with Dibenzyline.[13]

In our experiments "tolerance" has been demonstrated not to be associated with total cessation of sympathetic activity, since foot vasodilatation still followed acute injections of ganglionic blocking agents. In the muscular areas and possibly elsewhere, sympathetic vasomotor tone is apparently considerably reduced; if we can judge by forearm blood flow measurements before and during "tolerance," such reduction is not associated with an increase in resting blood flow in the "tolerant" patient. Hence some compensating mechanism has restored the vasoconstriction. Humoral substances such as epinephrine and norepinephrine have been excluded by the failure to note a fall in blood pressure following infusion of Dibenzyline in the tolerant patient (table 3). Adrenocortical activity might compensate although eosinophil counts do not give evidence of increased glucocorticoid excretion during "tolerance." The "cerebral pressor substance" of Taylor and Page[14] might play a role or the natural tendency of the vasculature to resume its "normal" contracted state might explain the restoration of normal muscle flow in the absence of sympathetic tone.

The situation would then resemble that in the totally sympathectomized hypertensive whose blood pressure is restored to high levels by unknown, probably intrinsic, compensations and who then fails to respond with a drop in blood pressure to ganglionic blocking agents. The chemically sympathectomized patient is still responsive to other vasodilators such as histamine and protoveratrine according to our observations, and it may be that with these other drugs, the refractory state may be overcome. In any event the failure of ganglionic blocking drugs to lower supine blood pressure, failures of sympathectomy and local denervations probably have their root in the nature of the compensatory mechanisms involved. It is to be hoped that further study of these reactions will lead to a better understanding of the role of sympathetic tone in hypertensive disease.

Conclusions

1. In man under chronic partial ganglionic blockade with hexamethonium, the usually depressor effects of intravenous tetraethylammonium and hexamethonium chloride in the supine position decrease and later become pressor.

2. During such a blockade, the resting foot and forearm blood flows, as studied in six cases, are not appreciably higher than the control values; the test injections elicit definite but less prominent increases in foot blood flow, indicating persistence of sympathetic tone to this area; the forearm blood flow response is considerably reduced, and increases in forearm flow are frequently observed, especially with hexamethonium.

3. Reasons are given for suggesting that the pressor action of tetraethylammonium chloride is a result of its direct vasoconstrictor action in the absence of a concomitant depressor effect.

4. Evidence is presented for exclusion of increases of sympathoadrenal and cortical hormones as the mechanism of tolerance, and other possibilities are discussed.

5. Cross tolerance developed between the various quaternary and tertiary-N ganglionic blocking agents studied (tetraethylammonium chloride, hexamethonium, pendiomide, SU-1194) and extended to a minor degree also to the adrenergic blocking agents Regitine and Dibenzyline.

Sumario Español

1. En el hombre sujeto a un bloqueo ganglionar crónico parcial con hexamethonium, los efectos usualmente depresores del cloruro de tetraetilamonio intravenoso y hexamethonium en la posición recostada disminuyen y luego se tornan en presores.

2. Durante tal bloqueo, la circulación del pié descansado y el antebrazo, según estudios en seis casos, no son apreciablemente más altos que los valores controles; las inyecciones de prueba produjeron aumentos definitivos pero menos prominentes en la circulación del pié,

indicando persistencia de tono simpático a esta área; la repuesta de la circulación del antebrazo estuvo considerablemente reducida y aumentos en el antebrazo fueron frecuentemente observados, especialmente con hexamethonium.

3. Se dan razones sugiriendo que la acción presora del cloruro de tetraetilamonio es un resultado directo de su acción vasoconstrictora en la ausencia de un efecto depresor concomitante.

4. Se presenta evidencia para excluir aumentos de hormonas simpatoadrenales y corticales como un mecanismo de tolerancia y otras posibilidades se discuten.

5. Tolerancia cruzada se desarrolló entre los varios agentes cuartenarios y terciarios-N bloqueadores ganglionicos estudiados (cloruro de tetraetiloamonio, hexamethonium, pendiomide, Su-1194) y se extendió en grado menor también a los agentes bloqueadores adrenérgicos Regitine y Dibenzyline.

REFERENCES

[1] La Due, J. S., Murison, P. J., and Pack, G. T.: The use of tetraethylammonium bromide as a diagnostic test for pheochromocytoma. Ann. Int. Med. **29:** 914, 1948.

[2] Page, I. H.: Mechanism of the vascular action of tetraethylammonium chloride. Am. J. Physiol. **158:** 403, 1949.

[3] Stone, C. A., Entwistle, G., and Loew, E. R.: Adrenal medullary stimulating action of tetraethylammonium. Proc. Soc. Exper. Biol. & Med. **78:** 358, 1951.

[4] Freyburger, W. A., Gruhzit, C. C., and Moe, G. K.: Pressor pathways not blocked by tetraethylammonium. Am. J. Physiol. **163:** 290, 1950.

[5] Dontas, A. S.: unpublished observations.

[6] Acheson, G. H., and Moe, G. K.: The action of tetraethylammonium ion on the mammalian circulation. J. Pharmacol. & Exper. Therap. **87:** 220, 1946.

[7] Teschendorf, W.: Über die Gefässwirkung organischer Kationen und ihre Beeinflussung durch anorganische Ionen. Biochem. Ztschr. **118:** 265, 1921.

[8] Kingsolver, W. R., Dontas, A. S., and Hoobler, S. W.: Bioassay of small amounts of vasoactive substances. J. Applied Physiol. **6:** 59, 1953.

[9] Brust, A. A., Ransohoff, W., and Reiser, M. F.: Blood pressure responses to ACTH and Cortisone in normotensive and hypertensive subjects in the resting state and during autonomic blockade with tetraethylammonium chloride. J. Clin. Investigation **30:** 630, 1951.

[10] Ray, B. S., and Console, A. D.: Evaluation of total sympathectomy. Ann. Surgery **130:** 652, 1949.

[11] Paton, W. D. M., and Zaimis, E. J.: Paralysis of autonomic ganglia by methonium salts. Brit. J. Pharmacol. **6:** 155, 1951.

[12] Morrison, B.: Parenteral hexamethonium in hypertension. Brit. M. J. **1:** 1291, 1953.

[13] Corcoran, A. C., Taylor, R. D., and Harrison, M.: Ineffectiveness of 688A (N-phenoxy-isopropyl-H-benzyl-beta-chloroethyl amine hydrochloride) in treatment of essential hypertension. Proc. Soc. Exper. Biol. & Med. **80:** 265, 1952.

[14] Taylor, R. D., and Page, I. H.: On the origin and properties of a cerebral pressor substance. Am. J. Physiol. **170:** 321, 1952.

Estrogen Inhibition of Corticoid Hypertension in Chickens

By J. STAMLER, M.D.

WITH THE TECHNICAL ASSISTANCE OF P. JOHNSON AND A. ELLIS

Estrogens tend to lower the blood pressure of cockerels. Estrogen-treated cockerels and estrogen-secreting hens are immune to the chronic pressor effects of desoxycorticosterone acetate (DCA) and cortisone.

BOTH desoxycorticosterone acetate (DCA) and cortisone effect moderate hypertension in cockerels.[1, 2] The present studies demonstrate that estrogen-treated cockerels and estrogen-secreting hens are immune to this corticoid-induced blood pressure elevation.

METHODS

The experimental designs and technics were generally in accord with the standardized procedures of the department.[5] Four series of experiments were accomplished varying in duration from five to nine weeks and utilizing a total of 95 chickens (table 1). In three series (BC 20, BC 31A and BC 31B), cockerels were utilized, and the effects of exogenous estrogens on corticoid hypertension assessed. In one series (BC 29), mature, gonadally active, egg laying hens were utilized, to determine whether desoxycorticosterone acetate would induce increased blood pressure in the presence of endogenous estrogen secretion. In two series (BC 29 and 31A), 1 per cent sodium chloride was incorporated in the feed, to increase the hypertensive effect of desoxycorticosterone acetate.[1] In two series (BC 20 and BC 31A), a cholesterol-supplemented mash was fed, since it was desired concomitantly to study atherogenesis.[6]

Blood pressure was determined on the unanesthetized quiescent bird, kept lying on its side on an animal board. A sciatic artery was isolated by blunt dissection and cannulated under direct visualization with a 20 gage needle, precautions being taken to eliminate blood loss. A Lilly electromanometer and Sanborn direct-writing twin Visocardiette were used to obtain and record blood pressure.

Unanesthetized birds were bled via a wing vein. The blood was immediately heparinized, centrifuged, and the plasma removed. Plasma sodium and potassium concentrations were determined with a Beckman flame photometer.

RESULTS

Blood Pressures. In three series of experiments with cockerels, estrogens consistently inhibited the pressor response to corticoids (table 2). Estrogens were equally effective in preventing the hypertensive action of desoxycorticosterone acetate, desoxycorticosterone acetate plus sodium chloride and cortisone. Estrogen administration tended generally to induce blood pressure levels lower than controls. In mature, gonadally active, egg laying hens, desoxycorticosterone acetate plus sodium chloride failed to effect a pressor response (table 3).

Plasma Electrolytes. Both groups of egg-laying hens exhibited levels of plasma potassium significantly lower than those of cockerels (series BC 29, table 4). In cockerels, desoxycorticosterone alone, estrogens alone, and desoxycorticosterone plus sodium chloride all produced significant moderate hypopotassemia. The combination of estrogens plus corticoid consistently induced more marked hypopotassemia. Plasma sodium levels were unaltered by the experimental regimens, except for two groups: In series BC 31A, desoxycorticosterone acetate plus sodium chloride plus estrogens (group 4) effected hypernatremia, whereas in

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

These studies were supported in part by the Michael Reese Research Foundation and by a grant from the National Heart Institute (H897).

Some of these findings were originally presented before the American Physiological Society[3] and the Second World Congress of Cardiology[4].

These studies were done during the tenure of a Fellowship as an Established Investigator of the American Heart Association.

TABLE 1.—*Experimental Regimens*

Series and Sex	Group	Number of Birds	Chick Age During Experiment (weeks)	Diet	Hormone*
BC20 ♂	1	6	12–19	1 CO†	None
	2	6	12–19	1 CO	Estrogens
	3	6	12–19	1 CO	DCA + Estrogens
	4	6	12–19	1 CO	Cortisone + Estrogens
BC29 ♀	1	5	22–31	PM† + 1% NaCl	None
	2	5	22–31	PM + 1% NaCl	DCA
BC31A ♂	1	8	9–16	PM	None
	2	6	9–16	1 CO	Estrogens
	3	11	9–16	1 CO + 1% NaCl	DCA
	4	10	9–16	1 CO + 1% NaCl	DCA + Estrogens
BC31B ♂	7	6	14–20	PM	DCA
	8	5	14–20	PM	DCA + Estrogens
	9	7	14–20	PM	Cortisone
	10	8	14–20	PM	Cortisone + Estrogens

* Hormone dosages were:

Estrogens (mixed conjugated equine estrogens)—minimum of 20 mg./chick/day in the drinking water.

DCA (desoxycorticosterone acetate in oil)—1 to 5 mg./chick/day parenterally.

Cortisone (saline suspension)—2 to 20 mg./chick/day parenterally.

† 1 CO is chick starter mash plus 1% cholesterol and 5% cottonseed oil. PM is plain (unsupplemented) chick starter mash.

TABLE 2.—*Blood Pressures of Cockerels*

Series	Group	Age (wks.)	Regimen	Systolic Pressure (mm. Hg)	Diastolic Pressure (mm. Hg)
BC20	1	19	1 CO Control	149† ± 3.2* 140–162‡	
	2	19	1 CO Estrogens	142 ± 3.3 134–156	
	3	19	1 CO DCA + Estrogens	150 ± 3.4 136–160	
	4	19	1 CO Cortisone + Estrogens	132 ± 6.7 116–162	
BC31A	1	14	PM Control	142 ± 4.9 125–152	119 ± 3.9 105–125
	2	14	1 CO Estrogens	137 ± 4.7 115–155	115 ± 4.0 95–125
	3	14	1 CO NaCl-DCA	159 ± 5.2 132–180	130 ± 3.9 103–147
	4	14	1 CO NaCl-DCA + Estrogens	135 ± 3.3 120–150	111 ± 2.8 95–125
BC31B§	7	20	DCA	161 ± 5.3 140–170	136 ± 3.5 125–140
	8	20	DCA + Estrogens	128 ± 3.7 120–140	109 ± 4.2 100–120
	9	20	Cortisone	164 ± 4.5 148–175	135 ± 4.2 120–143
	10	20	Cortisone + Estrogens	132 ± 6.6 115–158	113 ± 4.9 100–130

* Standard error (S.E.) of the mean.

$$\text{S.D.} = \sqrt{\frac{(\overline{X_i} - \overline{X})^2}{N - 1}}$$

$$\text{S.E.} = \frac{\text{S.D.}}{\sqrt{N}}$$

† These are mean blood pressures.

‡ Range.

§ In Series BC32 hatched 2 to 3 weeks after Series BC31B control cockerels (subsisting on plain mash and tap water *ad lib.*) exhibited these blood pressure findings: Systolic 138 ± 6.6 (range 114–150); diastolic 123 ± 6.6 (range 103–140).

series BC 31B, desoxycorticosterone plus estrogens (group 8) induced hyponatremia, both in association with marked hypopotassemia.

Other findings. All groups given estrogens, desoxycorticosterone acetate, desoxycorticosterone acetate plus sodium chloride, or estrogens plus corticoid tended to exhibit moderate polydypsia. Exhibition of corticoid or estrogens plus corticoid had little or no consistent effect on feed intake, growth or development; all birds, irrespective of hormone regimen, were well nourished and well developed.

DISCUSSION

These experiments conclusively demonstrate that estrogen-treated cockerels and estrogen-secreting hens are significantly resistant to the chronic pressor influences of corticoids. They indicate that estrogens specifically inhibit corticoid-induced hypertension in chickens. They further suggest that estrogens tend generally to lower blood pressure in this avian species.

Review of the literature reveals a paucity of previous work on the effects of estrogens on blood pressure homeostasis. It is known that the systolic blood pressure of roosters is 15 to 25 per cent higher than that of hens.[7, 8] Simultaneous with the initial presentation of our data,[3] it was reported independently that diethylstilbesterol lowers blood pressure in intact and caponized adult male chicks, an effect which gonadotrophin tends to reverse.[9]

Ten years ago, data were published from our department demonstrating that the blood pressure of normotensive and Goldblatt hyper-

TABLE 3.—*Blood Pressures of Hens (Series BC29)*

Group	Age (weeks)	Regimen	Systolic Pressure (mm. Hg)	Diastolic Pressure (mm. Hg)
1	22*	PM	151 ± 5.8‡ 135–170§	119 ± 3.7 110–130
2	22*	PM	144 ± 2.5 135–150	122 ± 5.5 106–138
1	31†	PM + 1% NaCl	160 ± 6.3 140–172	120 ± 3.1 110–125
2	31†	PM + 1% NaCl + DCA	155 ± 7.0 138–175	127 ± 4.7 110–136

* Data prior to institution of experimental regimen.

† Nine weeks on experimental regimen.

‡ Standard error of the mean.

§ Range.

TABLE 4.—*Plasma Electrolyte Concentrations*

Series and Sex	Group	Regimen	Plasma Na (mEq./L.)	Plasma K (mEq./L.)
BC29 ♀	1	PM + 1% NaCl	156.4 ± 1.3† 151.6–159.0*	2.63 ± 0.01 2.34–2.92
	2	PM + 1% NaCl + DCA	155.5 ± 2.0 151.0–161.6	2.49 ± 0.03 2.44–2.58
BC31A ♂	1	PM Control	157.2 ± 0.5 156.0–159.2	4.96 ± 0.24 4.04–5.74
	2	1 CO + Estrogens	156.9 ± 0.6 155.0–159.2	4.04 ± 0.12 3.56–4.40
	3	1 CO + NaCl − DCA	157.2 ± 1.3 153.0–161.0	4.59 ± 0.18 4.24–5.22
	4	1 CO + NaCl − DCA + Estrogens	166.3 ± 1.4 162.0–170.0	3.60 ± 0.11 3.40–4.14
BC31B ♂	7	PM + DCA	161.6 ± 1.5 157.0–166.6	4.26 ± 0.19 3.56–4.78
	8	PM + DCA + Estrogens	150.0 ± 4.1 132.6–162.0	3.49 ± 0.17 3.32–4.22
	9	PM + Cortisone	160.2 ± 1.6 156.6–165.0	4.74 ± 0.31 4.32–5.08
	10	PM + Cortisone + Estrogens	156.5 ± 1.8 151.0–162.0	4.27 ± 0.07 3.96–4.46

* Range. † Standard error of the mean.

tensive dogs tends to fall late in pregnancy.[10] More recently, it was reported that large doses of desoxycorticosterone acetate produce hypertension only in adult male dogs; no increase in blood pressure occurs in adult females.[11] This sex difference is not observed in immature dogs. Studies on the effects of estrogens on corticoid hypertensive dogs are currently in progress in our laboratory.

TABLE 5.—*Other Findings*

Series and Sex	Group	Regimen	H_2O Intake (cc.)	Feed Intake (Gm./chick/day)	Terminal Wt. (Gm.
BC20 ♂	1	1 CO Control	320*	143*	2278 ± 137 1867–2858
	2	1 CO + Estrogens	502*	136*	2316 ± 47 2208–2519
	3	1 CO + DCA + Estrogens	600*	121*	1909 ± 59 1697–2094
	4	1 CO + Cortisone + Estrogens	638*	167*	1839 ± 115 1472–2264
BC31A ♂	1	PM Control	125§	—	—
	2	1 CO + Estrogens	170§	—	—
	3	1 CO + NaCl − DCA	364§	—	—
	4	1 CO + NaCl − DCA + Estrogens	340§	—	—
BC31B ♂	7	PM + DCA	—	138*	2223 ± 99 2040–2700
	8	PM + DCA + Estrogens	—	222*	2063 ± 48 1900–2200
	9	PM + Cortisone	—	107*	1912 ± 202 1340–2600
	10	PM + Cortisone + Estrogens	—	178*	1953 ± 95 1600–2240

* Twenty-four hour intake; data were collected on the group as a unit.

† Standard error of the mean.

‡ Range.

§ Six hour intake, determined during seventh experimental week; data were collected on the group as a unit.

Data on the influence of estrogens on blood pressure of rats are contradictory. It was reported,[12-14] and denied,[15] that estradiol and diethylstilbesterol may induce hypertension in this species. More recently, data were published demonstrating that pregnancy does not inhibit the hypertension developing in rats treated with antiplacenta serum plus desoxycorticosterone acetate.[16] In another study, it was found that rats given estradiol plus desoxycorticosterone acetate frequently fail to develop the usual desoxycorticosterone acetate hypertension.[17] This was interpreted as a nonspecific response, attributable to general debility ensuing with the hormone combination. In view of our observations, further studies in the rat are definitely indicated.

At present, little is known concerning the mechanisms of estrogen effects on cardiovascular homeostasis. Estrogens are known to influence protein, lipid and calcium metabolism, with resultant alterations of plasma levels

f these substances.[5] Estrogens also suppress he secretion of anterior pituitary hormones[23] nd inhibit injury-induced connective tissue roliferation.[24-25] Further, they induce acute asodilatation in rabbit, rat and man.[15, 23] Additional work is necessary to elucidate the elationship, if any, between these estrogen ctions and estrogen inhibition of corticoid ypertension.

In the present experiments, estrogen inhibition of corticoid hypertension was invariably associated with significant lowering of plasma potassium levels. In view of other data relating altered water-electrolyte metabolism to the pathogenesis of hypertension, and demonstrating antihypertensive effects of both sodium and potassium depletion in rats, dogs, chicks and man,[1, 26-41] further work is essential to determine whether the concomitant effects of estrogens on water-electrolyte metabolism and on blood pressure homeostasis have any cause-and-effect inter-relationship.[46]

From recent studies, it is clear that a significant sex difference exists in incidence of human hypertension. Hypertension is more common in young men than in young women; after the age of 40, the reverse is true, hypertension being more common in females.[43, 44]

It is common knowledge that the female climacteric is "normally" associated with vasomotor instability, characterized by hot flushes and fluctuations in blood pressure. The older medical literature distinguishes a "menopausal hypertension," presumably developing immediately after artificial or natural menopause.[15, 43, 45] The actuality of this entity has been seriously challenged by more recent studies.[45] However, several contemporary classifiers identify endocrine types of hypertension, including a type or types in females associated with significant folliculoid-corticoid dysfunction.[42, 43] Therapeutic trials of estrogens in hypertension, particularly in menopausal women, have yielded contradictory results, with the bulk of workers reporting little or no positive response.[15, 23, 43, 45]

Our demonstration of the ability of estrogens to inhibit experimental corticoid-induced hypertension, together with numerous observations on the influences of estrogens on cardiovascular function of man and animals, inevitably provokes the speculative questions: Does the natural endogenous estrogen secretion tend to protect premenopausal woman against hypertension? Is there any role for estrogens in the therapy of human hypertension? Neither of these questions can be answered with finality at present. Both problems merit further exploration.

Summary

1. Estrogens tend to lower blood pressure of cockerels.

2. Both estrogen-treated cockerels and estrogen-secreting hens are specifically protected against hypertension induced by desoxycorticosterone acetate, desoxycorticosterone acetate plus sodium chloride, and cortisone.

3. Mature egg-laying hens exhibit low potassium levels.

4. Estrogen inhibition of corticoid hypertension is associated in both cockerels and hens with decreased concentrations of plasma potassium.

Sumario Español

1. Los estrógenos tienden a reducir la presión arterial en gallipollos.

2. Los gallipollos tratados con estrogeno y gallinas produciendo estrógeno son especificamente protegidas contra la hipertensión inducida por acetato de desoxicorticosterona, acetato de desoxyicorticosterona más cloruro de sodio y cortisona.

3. Gallinas adultas ponedoras de huevos exhiben niveles bajos de potasio.

4. La inhibición de la hipertensión corticoide por el estrógeno está asociada en ambos gallipollos y gallinas con concentraciones bajas de potasio en el plasma.

Acknowledgments

I am indebted to Drs. L. N. Katz, S. Rodbard and R. Pick for invaluable advice throughout the course of these experiments.

Drs. John B. Jewell and Stanley Jaros of Ayerst Laboratories, Drs. Augustus Gibson and Frederick K. Heath of Merck and Co., Inc., and Dr. Norman L. Heminway of the Schering Corp. contributed generous supplies of mixed conjugated equine estrogens (Premarin), cortisone (Cortone) and desoxycorticosterone acetate (Cortate) respectively.

Mr. A. Ellis accomplished the sodium and potassium flame photometric analyses. Messrs. G. Crowley and C. Jones also rendered excellent technical assistance.

REFERENCES

[1] STAMLER, J., PICK, R., AND KATZ, L. N.: Effects of desoxycorticosterone acetate on cholesterolemia, blood pressure and atherogenesis in chicks. Circulation **4:** 262, 1951.

[2] —, —, AND —: Effects of cortisone, hydrocortisone and corticotropin on lipemia, glycemia and atherogenesis in cholesterol-fed chicks. Circulation **10:** 237, 1954.

[3] —: Effects of sex and adrenal steroids on blood pressure in dog and chick. Federation Proc. **13:** 144, 1954.

[4] —: Hypertensive effects of adrenal corticoids and their prevention by estrogens. Proc., Second World Congress of Cardiology. In press.

[5] KATZ, L. N., AND STAMLER, J.: Experimental Atherosclerosis. Springfield, Ill., Charles C Thomas, 1953.

[6] STAMLER, J., PICK, R., AND KATZ, L. N.: Estrogen prophylaxis of cholesterol-induced coronary atherogenesis in chicks given adrenal corticoids or ACTH. Circulation **10:** 247, 1954.

[7] STURKIE, P. D., WEISS, H. S., AND RINGER, R. K.: Effects of age on blood pressure in the chicken. Am. J. Physiol. **174:** 405, 1953.

[8] —: Avian Physiology. Ithaca, N. Y., Comstock Publishing Associates, 1954.

[9] —, AND RINGER, R. K.: Effects of estrogen and gonadotrophins on blood pressure in the chicken. Federation Proc. **13:** 147, 1954.

[10] RODBARD, S., AND KATZ, L. N.: The effect of pregnancy on blood pressure in normotensive and hypertensive dogs. Am. J. Obst. Gynec. **47:** 753, 1944.

[11] DE MURO, P., AND ROWINSKI, P.: The role of sex in the hypertensive action of desoxycorticosterone acetate (DCA). Acta med. scandinav. **141:** 70, 1951.

[12] GROLLMAN, A., HARRISON, T. R., AND WILLIAMS, J. R., JR.: The effect of various sterol derivatives on the blood pressure of the rat. J. Pharmacol. Exper. Therap. **69:** 149, 1940.

[13] LEATHEM, J. H., AND DRILL, V. A.: The effect of diethylstilbestrol on the blood pressure of normal and hypophysectomized rats. Am. J. Physiol. **139:** 17, 1943.

[14] SAPEIKA, N.: Adrenal cortex and arterial hypertension. Arch. Int. Med. **82:** 263, 1948.

[15] SELYE, H.: Textbook of Endocrinology. Montreal, Acta Endocrinologica, 1947.

[16] LOEB, E. N., KNOWLTON, A. I., STOERK, H. C., AND SEEGAL, B. C.: Observations on the pregnant rat injected with nephrotoxic rabbit anti-rat placenta serum and desoxycorticosterone acetate. J. Exper. Med. **89:** 287, 1949.

[17] FRIEDMAN, S. M., AND FRIEDMAN, C. L.: A screening test to indicate opposition to the cardiovascular-renal effects of desoxycorticosterone acetate in the rat: The effect of adrenal cortical extract. Endocrinology **46:** 367, 1950.

[18] PICK, R., STAMLER, J., RODBARD, S., AND KATZ, L. N.: The inhibition of coronary atherosclerosis by estrogens in cholesterol-fed chicks. Circulation **6:** 276, 1952.

[19] —, —, —, AND —. Estrogen-induced regression of coronary atherosclerosis in cholesterol-fed chicks. Circulation **6:** 858, 1952.

[20] STAMLER, J., PICK, R., AND KATZ, L. N.: Prevention of coronary atherosclerosis by estrogen-androgen administration in the cholesterol-fed chick. Circulation Research **1:** 94, 1953.

[21] —, —, AND —. Inhibition of cholesterol-induced coronary atherogenesis in the egg-producing hen. Circulation **10:** 251, 1954.

[22] —, — AND —: Further studies on estrogen prophylaxis of cholesterol-induced coronary atherogenesis. Circulation **8:** 436, 1953.

[23] BURROWS, H.: Biological Actions of Sex Hormones, ed. 2. Cambridge, England, Cambridge University Press, 1949.

[24] TAUBENHAUS, M., AND AMROMIN, G. D.: The effects of the hypophysis, thyroid, sex steroids, and the adrenal cortex upon granulation tissue. J. Lab. Clin. Med. **36:** 7, 1950.

[25] —, TAYLOR, B., AND MORTON, J. V.: Hormonal interaction in the regulation of granulation tissue formation. Endocrinology **51:** 183, 1952.

[26] RODBARD, S., AND FREED, S. C.: The effect of desoxycorticosterone acetate on the blood pressure of the dog. Endocrinology **30:** 365, 1942.

[27] FRIEDEN, J., STAMLER, J., HWANG, W., KURAMOTO, K., AND KATZ, L. N.: Effect of chronic salt depletion on blood pressure of renal hypertensive dogs. Am. J. Physiol. **168:** 500, 1952.

[28] STAMLER, J., HWANG, W., AND KURAMOTO, K.: Renal clearances of sodium and chloride in Goldblatt hypertensive dogs. Am. J. Physiol. **165:** 328, 1951.

[29] —, AND MININNI, G.: Fluid exchange during incipient nephrogenic hypertension in dogs. J. Lab. & Clin. Med. **40:** 946, 1952.

[30] LENEL, R., KATZ, L. N., AND RODBARD, S.: Arterial hypertension in the chicken. Am. J. Physiol. **152:** 557, 1948.

[31] STAMLER, J., AND KATZ, L. N.: The effect of "salt" hypertension on atherosclerosis in chicks fed mash without a cholesterol supplement. Circulation **3:** 859, 1951.

[32] RODBARD, S.: Blood pressure regulatory mechanisms and salt water exchanges. Proc., Annual Meeting, Council for High Blood Pressure Research, Am. Heart A. **2:** 42, 1954.

[13] Proc., Annual Meeting, Council for High Blood Pressure Research, Am. Heart A. **2:** 1954.

[14] GREEN, D. M.: Hypertension. In Selye, H., and Horava, A.: Third Annual Report on Stress, Acta, Montreal, 1953. P. 277.

[15] BELL, E. T., ed.: Hypertension—A Symposium. Minneapolis, University of Minnesota Press, 1951.

[16] FREED, S. C., AND FRIEDMAN, M.: Depressor effect of potassium restriction on blood pressure of the rat. Proc. Soc. Exper. Biol. & Med. **78:** 74, 1951.

[17] ROSENMAN, R. H., FREED, S. C., AND FRIEDMAN, M.: Effect of variation of potassium intake on pressor activity of desoxycorticosterone. Proc. Soc. Exper. Biol. & Med. **78:** 77, 1951.

[18] FRIEDMAN, M., ROSENMAN, R. H., AND FREED, S. C.: Depressor effect of potassium deprivation on the blood pressure. Am. J. Physiol. **167:** 457, 1951.

[39] KEMPNER, W.: Treatment of hypertensive vascular disease with rice diet. Am. J. Med. **4:** 545, 1948.

[40] WATKIN, D. M., FROEB, H. F., HATCH, F. T., AND GUTMAN, A. B.: Effects of diet in essential hypertension. Am. J. Med. **9:** 441, 1950.

[41] PERERA, G. A.: Depressor effects of potassium deficient diets in hypertensive man. J. Clin. Investigation **32:** 633, 1953.

[42] PAGE, I. H., AND CORCORAN, A. C.: Hypertension and the problem of vascular homeostasis. Circulation **6:** 286, 1952.

[43] SCHROEDER, H. A.: Hypertensive Diseases. Philadelphia, Lea & Febiger, 1953.

[44] MASTER, A., GARFIELD, C. I., AND WALTERS, M. B.: Normal Blood Pressure and Hypertension. Philadelphia, Lea & Febiger, 1952.

[45] FISHBERG, A. M.: Hypertension and Nephritis, eds. 4 and 5. Philadelphia, Lea & Febiger, 1939 and 1954.

[46] STAMLER, J. KATZ, L. N., AND PICK, R.: Nutritional-endrocrinological interrelationships in the pathogenesis of hypertension and atherosclerosis over the life span. In Selye, H., and Horava, A.: Fourth Annual Report on Stress. Montreal, Acta. In press.

[47] FISHER, R. A.: Statistical Methods for Research Workers, Edinburgh, Oliver and Boyd, 1948, (10th ed.).

The Effect of Congestive Heart Failure on Blood Volume as Determined by Radiochromium-Tagged Red Cells

By SEYMOUR EISENBERG, M.D.

WITH THE TECHNICAL ASSISTANCE OF MISS MARY SUE MCCALL

Total blood volume, red cell mass and plasma volume have been determined with radiochromium in subjects with congestive heart failure, before and after treatment. All functions were significantly increased during the congestive state and all decreased as compensation was achieved. The magnitude of the hypervolemia and the changes incident to treatment were apparently related to alterations in heart size. Selective expansion of the plasma volume was not encountered.

THE effect of congestive heart failure on total blood volume and circulating red cell mass remains a matter of considerable controversy. Studies with T-1824 dye[1-4] have yielded uniformly increased values, but the accuracy of the method has been vigorously challenged by Peters,[5] Ross,[6] and others.[7-10] It is likely that these measurements include an expanded lymphatic space, thereby yielding falsely high values. On the other hand, measurements utilizing radiophosphorous-labeled red cells[6, 11-13] have yielded conflicting results, but the instability of the P^{32}-red cell complex does not permit prolonged equilibration periods and is perhaps not accurate in subjects with congestive heart failure.

Determination of total blood volume and red cell mass utilizing radiochromium-tagged red cells as a reference avoids the above defects. The objection to the dye method would not pertain, and the stability of the Cr^{51}-red cell complex permits prolonged periods for equilibration. Thus, Sterling and Gray[14] established the constancy of the measured red cell mass for a 24-hour period, and similar observations have been made in our laboratory.[15]

The present study was undertaken to elucidate the problem of changes in blood volume in patients with congestive heart failure by the application of the radiochromium technic. Blood volumes were determined in the congestive state and again after optimum compensation had been achieved. The results were analyzed in the following ways: Comparisons were made between the pretreatment and post-treatment values and between these values and those of a group of 20 normal subjects. In this way information was provided regarding the intravascular volume in congestive heart failure and the changes which might occur following treatment. In addition, the results in patients with varying degrees of congestive failure were analyzed separately.

From the Department of Internal Medicine of the Southwestern Medical School of the University of Texas, and the Medical Service and Radioisotope Unit of the Veterans Administration Hospital, Dallas, Tex.

MATERIAL AND METHODS

Twenty-seven patients with congestive heart failure were studied. The diagnosis was established when the characteristic history of heart disease and heart failure was elicited and the physical findings of pulmonary congestion, edema, cardiac enlargement, hepatomegaly, and venous distention were present. Following clinical evaluation, the initial blood volume was determined. Appropriate therapy was then initiated; digitalis alone was first administered; diuretic measures were added if necessary. Response to treatment was carefully noted, and the determination of blood volume was repeated after optimum compensation had been achieved.

The pertinent clinical information is summarized in table 1. The patients were divided into categories according to the severity and duration of their disease. Preliminary observations indicated consistent group differences of sufficient magnitude to justify the classification. The patients with congestive heart failure of "mild" degree had, in the main, only

TABLE 1.—*Summary of the Pertinent Clinical Data on Twenty-Six Subjects with Congestive Heart Failure*

Patient	Diagnosis	Duration of Symptoms	"Dry" Wt.* Kg.	Wt. loss with Treat. Kg.	Initial V.P. mm. saline	Initial Decholin C.T. secs.	Initial Card. Enlarg.†	Max. Serum Bilirubin during Treat. mg.	Remarks
Mild Failure Group									
A. G. D. 60	H.C.V.D.	3 mos.	68	3.6	180	24	++	.4	Sympt. predominantly of l. ventric. fail. Prompt response to treat.
W. A. T. 55	R.H.D. A.I., M.S.	8 mos.	61	7.2	220	21	+++		Initial episode; slow response to treatment.
W. W. I. 64	A.S.H.D.	2 mos.	60	3.2	190	36	++	.8	Prompt response to digitalis.
L. R. K. 40	Idiopath. Myocard.	4 wks.	53	11.9	240	55	++	.7	Dramatic response to digitalis but gallop rhythm persists; congest. fail. has recurred.
P. B. 53	A.S.H.D.	10 days	53	2.7	200		++		Recent onset of auric. fib.; fairly prompt response to digitalis; mod. emphysema.
Moderate Failure Group									
C. N. O. 40	Idiopath. Myocard.	1 yr.	80	8.6	280	26	+++		Chron. alcoholic; deficient diet; gallop rhythm for 2 years; repeated decomp.; poorly controlled.
A. M. 52	A.I., Syph.	6 mos.	54	2.3	79	30	+++		Progressive, intractable fail.; expired 6 months later.
A. T. 63	H.C.V.D.	7 yrs.	72	8.6	260	70	+++	.8	Prompt response to digitalis.
C. L. B. 39	H.C.V.D.	1 yr.	61	12.2	320	52	+++	.4	Prompt response to digitalis.
H. C. H. 60	H.C.V.D.	? 3 wks.	63	15	280	60	++++	.7	Prompt response to digitalis. Aphasia and mental confusion.
L. C. 53	H.C.V.D.	2 yrs.	91	3.6	320	25	+++	.5	Obese; symptoms predominantly of l. ventric. fail.; adequate response to treat.
R. E. H. 59	H.C.V.D.	7 yrs.	82	7.2	254	45	++++	.5	Prompt response to digitalis.
J. B. 58	A.S.H.D.	2 mos.	50		260	19	++		Massive anasarca; expired 3 days after admission.
J. N. C. 63	R.H.D. M.S.	1 yr.	57	2.7	98	Uns.	+++		Sympt. predominantly of l. ventric. fail.; responded promptly to digitalis. Slight emphysema.
W. D. 67	A.S.H.D.	2 yrs.	59	7.2	260	45	++++	4.3	Prompt response to digitalis. Developed icterus during treat.
S. E. D. 64	A.S.H.D.	6 yrs.	53	5.9	185	Uns.	++	.3	Prompt response to digitalis.

TABLE 1—*Continued*

Patient	Diagnosis	Duration of Symptoms	"Dry" Wt.* Kg.	Wt. loss with Treat. Kg.	Initial V.P. mm. saline	Initial Decholin C.T. secs.	Initial Card. Enlarg.†	Max. Serum Bilirubin during Treat. mg.	Remarks
				Severe Failure Group					
W. J. 54	A.S.H.D.	8 yrs.	64		220	60+	++++		Intractable fail.; expired after first study.
S. R. 62	A.S.H.D.	3 yrs.	55	18.2	180	18	++++	.9	Slow and inadequate response to treat.; expired.
J. D. 61	Aneurysm A.I., Syph.	3 yrs.	73	11.3	150	Uns.	++++		Intractable fail. Expired.
L. F. 64	Aneurysm A.I., Syph.	2 yrs.	64	17	420	25	++++		Never rendered symptom free; V.P. remained elevated. Unexplained anemia. Expired.
R. M. 57	A.S.H.D.	4 yrs.	67		242	55	++++		Poor response to treatment; no change in V.P.; expired.
R. A. R. 56	A.S.H.D.	6 yrs.	62		N.D.	N.D.	++++		Intractable fail.; studied at time of optimum compensation. Expired.
C. H. S. 52	A.S.H.D.	3 yrs.	54.5	4.5	180	35	++++	.4	Slow response to treat.; probable pulmon. infarc.
W. A. R. 60	A.S.H.D.	2 yrs.	52.4	5.9	176	40	++++	.5	Responded slowly to treat.; required intermittent mercurial injections.
F. M. 56	H.C.V.D.	3 yrs.	67	33	254	35	++++	3.1	Massive anasarca; slow but satisfactory response to treat.; developed icterus during treat.
L. J. 61	Syph. ostial stenosis	8 mos.	50		150	40	+++	.8	Studied after treat.; response slow and inadequate. Expired (apparently of myocard. ischemia).
J. S. B. 64	H.C.V.D.	8 yrs.	59	9	220	Uns.	++++	.5	Slow but satisfactory response to treat. Required intermittent mercurial injections. Expired.

Abbreviations: A.S.H.D., arteriosclerotic heart disease; A.I., aortic insufficiency; M.S., mitral stenosis; H.C.V.D., hypertensive cardiovascular disease; R.H.D., rheumatic heart disease; V.P., venous pressure; C.T., circulation time.

* "Dry" Weight: The patient's weight after complete delivery of edema fluid.

† Initial cardiac enlargement: The degree of cardiac enlargement was roughly quantitated without reference to actual measurements. + indicates minimal cardiac enlargement; ++ and +++ indicate intermediate degrees of enlargement; ++++ indicates extreme cardiac enlargement.

modest quantities of edema and had been symptomatic for a period of only several months. These patients responded promptly to digitalis and required neither diuretic measures nor rigid salt restriction. Patients with congestive failure of "moderate" degree were somewhat more edematous and had experienced repeated episodes of decompensation; they could still be treated with digitalis alone but responded rather slowly. The patients with "severe" congestive heart failure were either those with massive edema who required aggressive diuretic therapy or patients who were in a fairly steady state but who required intermittent mercurial injections to remain edema-free. The majority of these severely decompensated patients had been ill for several years, had experienced repeated episodes of con-

gestive failure and were now considered to have reached the point where actual "compensation" was no longer possible. Eight of the 11 patients in this group have since died.

Blood Volume. Blood volume was measured by the method of Sterling and Gray[14] as modified in our laboratory[15]; the patients were at complete bed rest during the entire procedure. Sixty-five cc. of whole venous blood were separated by centrifugation. The red cells were incubated with gentle agitation at 37 C. for one hour with 300 microcuries of Cr^{51} ($Na_2Cr^{51}O_4$). After three washings, the labeled red cells were mixed with the original plasma, and 45 cc. of the reconstituted whole blood were injected intravenously. The initial venous blood sample was withdrawn without stasis three hours later, and the blood volume was calculated by dividing the total counts injected by the counts per cubic centimeter of the three-hour sample. Whole blood samples were counted for 15 minutes in a Texas Deep Well Counter. Circulating red cell mass was estimated by multiplying the total blood volume by the venous hematocrit. The plasma volume was the difference between the total blood volume and the red cell mass.

The accuracy of the procedure used to measure the blood volume requires comment. In repeated studies on normal subjects the error of the blood volume determination was found to be less than 4 per cent. To avoid changes induced by this variation, particular attention will be devoted to alterations greater than 10 per cent. Values expressed as cubic centimeters per kilogram were calculated on the basis of the ultimate edema-free weight for the reason that edema fluid merely represents an increment in the extracellular fluid compartment and does not contribute to true body mass.

The plasma volume was not measured directly because direct measurements of this space depend on the use of labeled protein as a reference substance. Since the protein thus labeled penetrates into the lymphatic system, the volume of distribution of labeled protein includes not only the plasma space but a fraction of the extravascular space as well. In normal subjects during a rigid steady state this extravascular penetration may be of small magnitude and constant in amount. However, Peters[5] has emphasized that the vascular tree may be more pervious to protein during congestive heart failure, and it is likely that the volume and rate of flow in the lymphatic system would vary markedly, especially when salt is being retained or lost at rapid rates. Under these circumstances, measurements of the "labeled protein space" cannot be interpreted as representing plasma volume alone; the errors are such as to yield consistently false high values.

By estimating the plasma volume from the red cell mass and the venous hematocrit, the defects of a plasma label can be circumvented. This, of course, raises the question as to the validity of the venous hematocrit as an index of total body hematocrit. It has been shown by Chaplin, Mollison, and Vetter[16] that the ratio of venous hematocrit to total body hematocrit remains constant over wide variations in hematocrit range; further, they point out that the small vessel hematocrit would have to change markedly to induce serious errors in the total blood volume and plasma volume values. It is, therefore, the recommendation of this group that in congestive heart failure the plasma volume and total blood volume be estimated from the red cell mass and the venous hematocrit rather than from direct measurements of the plasma space.

Hematocrits. The packed cell volume was determined, using Wintrobe tubes and a centrifuge having a radius of 15 cm. from the spindle center to the bottom of the hematocrit tube. The tubes were spun for 60 minutes at 2400 revolutions per minute (647 gravities). No correction factors were applied.

Serum Bilirubin. Serum bilirubin was determined by the method of Malloy and Evelyn.[17]

Heart Size. Cardiac enlargement was estimated from 7-foot posteroanterior roentgenograms of the chest. Changes in heart size following treatment were roughly quantitated by superimposition of pretreatment and posttreatment roentgenograms; particular attention was devoted to comparisons of the depth of inspiration and other variables.

Results

The results are summarized in tables 2 and 3. In table 2, comparisons are made between the findings in patients with congestive heart failure (during decompensation and after compensation had been restored) and control subjects; values are expressed as cubic centimeters per kilogram, calculated on the basis of the "edema-free" weight. In table 3, comparisons are made between the pretreatment and post-treatment measurements; differences are expressed in cubic centimeters and as per cent change from the initial values.

Blood Volume, Red Cell Mass, and Plasma Volume in Untreated and Treated Congestive Heart Failure, Compared with Normal Subjects

Table 2 includes the mean values for the measured functions in the series of normal subjects. The range of values in the normal series is as follows: For blood volume, from 46 to 80 cc. per kilogram; for red cell mass, from 20.7 to 33.7 cc. per kilogram; for plasma volume, from 29.7 to 49.4 cc. per kilogram.

TABLE 2.—*A Comparison of Blood Volume, Red Cell Mass, and Plasma Volume in Patients with Congestive Heart Failure, before and after Treatment, with Normal Values*

	Wt. loss in Kg.	B.V. cc./Kg.*	R.C.M. cc./Kg.	P.V. cc./Kg.	B.V. cc./Kg.	R.C.M. cc./Kg.	P.V. cc./Kg.
		20 Normal Males					
Mean		66.3	27.8	38.6			
S. D.		8.67	3.27	6.41			
		Decompensated			Compensated		
		Mild Failure Group					
A. G. D.	3.6	59	29	30	60	30	30
W. A. T.	7.2	73	29	44	75	28	47
W. W. I.	3.2	76	32	44	66	30	36
L. R. K.	11.9	93	36	57	73	29	44
P. B.	2.7	87	33	54	70	30.5	39.5
Mean		77.6	31.8	45.8	68.7	29.4	39.2
S. D.		13.01	2.94	10.59	5.92	1.13	6.68
p.		>.1	<.02	>.4	>.1	>.1	>.7
		Moderate Failure Group					
C. N. O.[1]	8.6	72	37	35	74	38	36
C. N. O.[2]		76	38	38			
A. M.	2.3	73	31	42	80	34	46
A. T.	8.6	87	39	48	75	34	41
C. L. B.	12.2	76	33	43	60	32	28
H. C. H.	15	87	39	48	80	37	44
L. C.	3.6	64	28	36	60	26	33
R. E. H.	7.2	67	32	35	66	32	34
J. B.		75	33	42			
J. N. C.	2.7	72	32	40			
W. D.	7.2	75	28	47	60	26	34
S. E. D.	5.9	81	28	53	65	24	39
Mean		75.4	33	42.3	70	31.4	37.2
S. D.		6.95	4.2	5.82	8.45	5.02	5.76
p.		<.01	<.01	>.1	>.1	>.1	>.1
		Severe Failure Group					
W. J.		84	39	45			
S. R.	18.2	85	42	43	86	39	47
J. D.	11.3	104	50	54	105	50	55
L. F.	17.0	97	34	63	95	33	62
R. M.		81	38	43	82	36	46
R. A. R.					92	44	48
C. H. S.	4.5	84	38	46	73	32	41
W. A. R.	5.9	95	35	60	87	32	55
F. M.	33.0	100	45	55	79	37	42
L. J.					83	34	49
J. S. B.	9.0	81	32	49	73	28	45
Mean		90.1	39	50.89	85.5	36.5	48.9
S. D.		8.86	5.67	7.44	9.93	6.46	6.53
p.		<.001	<.001	<.001	<.001	<.001	<.001
		All Groups					
Mean		81	35	45.9	75.8	33.14	42.6
S. D.		11	5.43	8.1	11.83	5.85	8.2
p.		<.001	<.001	<.01	<.01	<.001	>.1

* Cubic centimeters per kilogram was calculated on the basis of the "edema-free" weight, regardless of the presence or absence of edema.

TABLE 3.— *Individual Comparisons of Blood Volume, Red Cell Mass, and Plasma Volume Before and After Treatment in Patients with Congestive Heart Failure*

	B.V.[1] cc.	B.V.[2] cc.	Diff. cc.	% Change	R.C.M.[1] cc.	R.C.M.[2] cc.	Diff. cc.	% Change	P.V.[1] cc.	P.V.[2] cc.	Diff. cc.	% Change	Hct.[1] mm.	Hct.[2] mm.	Diff. mm.	Decrease in Heart Size*
Mild Failure Group																
A.G.D.	3996	4070	+74	+1.8	1990	2019	+29	+1.4	2006	2051	+45	+2.2	50	50	0	Marked
W.A.T.	4466	4482	+16	+.4	1755	1714	−43	−2.4	2711	2770	+59	+2.2	39	38	−1	Slight
W.W.I.	4530	3940	−590	−13.0	1900	1825	−75	−4.0	2630	2115	−515	−19.6	42	46	+4	Moderate
L.R.K.	4950	3850	−1100	−22.2	1930	1510	−420	−21.7	3020	2340	−680	−22.5	39	39	0	Moderate
P.B.	4580	3720	−860	−18.8	1730	1620	−110	−6.3	2850	2100	−750	−26.3	38	44	+6	Moderate
Mean			−492	−11.2			−124	−6.6			−368	−12.8			+1.8	
S.D.			522.9	9.8			54.8	8.89			393	13.9			3.03	
p.			>.1	>.1			<.02	>.1			>.1	>.1			>.2	
Moderate Failure Group																
C.N.O.	5775	5980	+205	+3.5	2951	3013	+62	+2.1	2824	2967	+143	+5.1	51	52	+1	Moderate
A.M.	3950	4325	+375	+9.5	1659	1816	+157	+9.4	2291	2509	+218	+9.5	42	42	0	None
A.T.	6280	5400	−880	−14.0	2820	2430	−390	−13.8	3460	2970	−490	−14.2	45	45	0	Marked
C.L.B.	4620	3640	−980	−21.2	2010	1944	−66	−3.3	2610	1696	−914	−35.0	44	53	+9	Marked
H.C.H.	5520	5100	−420	−7.6	2480	2340	−140	−5.6	3040	2760	−280	−9.2	45	46	+1	Marked
L.C.	5850	5450	−400	−6.8	2530	2420	−110	−4.35	3320	3030	−290	−8.7	43	45	+2	Slight
R.E.H.	5500	5420	−80	−1.4	2585	2600	+15	+.6	2915	2820	−95	−3.3	47	48	+1	Slight
W.D.	4430	3550	−880	−19.8	1672	1530	−142	−8.5	2758	2020	−738	−26.8	38	43	+5	Marked
S.E.D.	4298	3470	−828	−19.2	1470	1384	−86	−5.8	2828	2086	−742	−26.2	32	37	+5	Moderate
Mean			−432	−8.5			−77.77	−3.25			−354.2	−12.09			+2.55	
S.D.			598.8	10.93			154.1	6.67			612.7	15.01			3.17	
p.			>.05	<.05			>.05	>.1			>.05	<.05			<.05	
Severe Failure Group																
S.R.	4594	4775	+181	+3.9	2228	2134	−94	−4.1	2366	2641	+275	+11.6	48	45	−3	None
J.D.	7580	7640	+60	+.79	3590	3540	−50	−1.4	3990	4100	+110	+2.8	47	46	−1	None
L.F.	5954	5704	−250	−4.2	2149	2076	−73	−3.4	3805	3628	−177	−4.7	36	36	0	None
R.M.	5420	5540	+120	+2.2	2540	2420	−120	−4.7	2880	3120	+240	+8.3	47	44	−3	None
C.H.S.	4580	4000	−580	−12.6	2030	1730	−300	−14.8	2550	2270	−280	−11.0	44	43	−1	Moderate
W.A.R.	4920	4560	−360	−7.3	1835	1680	−155	−8.4	3085	2880	−205	−6.6	37	37	0	Slight
F.M.	6750	5280	−1470	−21.8	3030	2480	−550	−18.2	3720	2800	−920	−24.7	45	47	+2	Marked
J.S.B.	4770	4320	−450	−9.4	1860	1650	−210	−11.3	2910	2670	−240	−8.2	39	38	−1	Moderate
Mean			−343.6	−6.05			−194	−8.29			−149.6	−4.06			−.87	
S.D.			543.3	8.63			165	5.97			382.1	11.6			1.45	
p.			>.1	>.05			<.05	<.01			>.3	>.3			>.1	
All Groups																
Mean			−414	−8.26			−131	−5.85			−283	−9.33			+1.2	
S.D.			498	9.63			163	7.01			387	13.57			2.98	
p.			<.001	<.001			<.01	<.001			<.001	<.01			>.1	

B.V.[1], R.C.M.[1], P.V.[1], Hct.[1]: Blood volume, red cell mass, and plasma volume prior to treatment.
B.V.[2], R.C.M.[2], P.V.[2], Hct.[2]: Blood volume, red cell mass, and plasma volume following treatment.
* Changes in heart size have been quantitated by superimposition of pretreatment and posttreatment x ray films of the chest.

As compared with normal subjects, the blood volume, red cell mass, and plasma volume were significantly expanded in subjects with *severe* congestive heart failure ($p < 0.001$). Following treatment, the measurements of blood volume, red cell mass, and plasma volume remained significantly greater than those of the normal group ($p < 0.001$), although all of the measured functions decreased in four of the subjects (F.M., J.S.B., W.A.R., C.H.S.).

In congestive heart failure of *moderate* degree the measurements of blood volume and red cell mass were significantly greater than normal ($p < 0.01$) prior to treatment, but the plasma volume values did not differ significantly from those of the normal group

($p > 0.05$). The nine "compensated" patients in this group did not differ significantly from the normal group in any of the measured functions ($p > 0.05$).

In subjects with *mild* congestive failure there was a significant increase in red cell mass ($p < 0.05$); otherwise, there were no significant differences from the normal group.

The mean values for blood volume, red cell mass, and plasma volume in the 27 subjects in the combined groups, both before and after treatment, were significantly greater than the values for the normal group. The p value for the blood volume difference was <0.001 prior to treatment and <0.01 following treatment; the p value for the red cell mass difference was <0.001, both before and after treatment; the p value for the plasma volume difference was <0.01 prior to treatment and was <0.05 following treatment.

Individual Comparisons of Blood Volume, Red Cell Mass, and Plasma Volume Before and After Treatment

Table 3 includes 22 patients who were studied before and after treatment. The actual pretreatment and post-treatment measurements in each individual are compared; the values are not referred to body mass and are not compared with those of the normal group. Roentgenographic changes in heart size are roughly quantitated and are included in this table for convenience.

In the *severe* failure group there was a significant ($p < 0.01$) decrease in red cell mass as compensation was restored; blood volume and plasma volume were not significantly altered. In the *moderate* group there was a significant decrease in the total blood volume ($p < 0.05$) and plasma volume ($p < 0.05$) and a significant increase in hematocrit ($p < 0.05$). In the *mild* group there was a significant decrease ($p < 0.02$) in red cell mass following treatment. In the combined groups—including all of the 22 patients studied before and after treatment—total blood volume, red cell mass and plasma volume decreased significantly ($p < 0.001$) as compensation was achieved.

Discussion

The results of this study indicate that in congestive heart failure there is an expanded blood volume which may or may not decrease as compensation is achieved. Assuming the method to be accurate and the sample to be representative of the cardiac population, the crucial issues are the nature of the hypervolemia, the significance of the apparently progressive increase in blood volume as congestive failure becomes more severe, the discrepant effects of therapy on the volume of blood, and the role of hypervolemia in the pathogenesis of the disorder.

The nature of the hypervolemia is rather clearly defined. Comparison of 27 observations on "decompensated" patients with the normal group reveals that there was a 22 per cent increase in blood volume, a 25 per cent increase in red cell mass, and a 17 per cent increase in plasma volume. In every subject the red cell mass was greater than the mean for the normal group; in 12 instances the values exceeded the normal range. On the other hand, only seven measurements of plasma volume exceeded the normal range and five were less than the normal mean. It may be concluded, therefore, that there is no selective expansion of the plasma volume; the primary disorder is apparently an actual secondary polycythemia with inconsistent alterations in the volume of plasma.

The severity of the congestive process and the magnitude of the hypervolemia appeared to be definitely correlated. The expansion of the blood volume was not related to the quantity of edema fluid, the height of the venous pressure, or the etiology of the heart disease. However, both the severity of the congestive process and the magnitude of the increment in blood volume were paralleled by the degree of cardiac enlargement. In patients with congestive failure of *mild* degree the heart was only moderately enlarged; the mean value for blood volume in this group exceeded the mean for the normal group by 14 per cent. In patients with *severe* congestive failure the heart was markedly enlarged and the mean value for blood volume was 38 per cent greater than the normal mean. It is, therefore, sug-

gested that the hypervolemia is related to the degree of cardiac enlargement, which probably reflects an increase in the capacity of the central vascular bed (heart, great vessels, and pulmonary vascular tree). The expansion of the blood volume and the manifestations of salt retention and venous distention were not related.

Changes in blood volume incident to the correction of the congestive state have never been satisfactorily elucidated. Measurements before and after treatment with T-1824 dye have consistently indicated a significant contraction of the blood volume as compensation was restored. Measurements with P^{32}-labeled red cells have yielded conflicting results. Nylin[11] and Hedlund[13] reported definite shrinkage of the red cell mass after compensation was restored, whereas Ross and his group[6] could demonstrate no significant alterations following treatment.

In the 22 subjects in the present series, studied during the congestive state and again after optimum compensation had been achieved, a significant decrease in blood volume occurred as compensation was restored. However, there was marked inconsistency in the alterations of the blood volume following treatment. In 50 per cent of the patients the blood volume remained unchanged, whereas in the remainder, treatment apparently induced decrements in blood volume of considerable magnitude.

In nine subjects* the blood volume remained the same or increased slightly following treatment. Five† of the nine patients died of progressive congestive heart failure after the completion of the study; in none of the five was there a decrease in heart size or complete relief of respiratory symptoms despite the apparent delivery of all edema fluid. In three patients the size of the heart remained unchanged following treatment, although the response to treatment was satisfactory. In one patient there was a prompt response to treatment and a definite decrease in heart size. It is apparent, then, that patients can be delivered of all of their edema and rendered essentially symptom-free with no change in blood volume if the heart size remains unchanged.

In nine subjects‡ the blood volume following treatment decreased 10 per cent or more. This included plasma volume and red cell mass in four instances and plasma volume alone in five. As opposed to the previous group, the response to therapy was salutary in every instance; a prompt diuresis, complete relief of respiratory symptoms, and a decrease in venous pressure to normal invariably ensued; a definite decrease in heart size occurred in every instance.

A decrease in blood volume following treatment apparently occurs only when there is a decrease in the size of the heart. Disproportionate loss of plasma volume occurred in only 5 of the 22 subjects. The magnitude of the edema and the decrement in plasma volume were not correlated, as large volumes of edema fluid can be delivered without significant change in plasma volume. Selective loss of red cell mass was not encountered, although significant decrements did occur in conjunction with loss of plasma volume in four subjects. The fate of the "lost" red cells was not apparent, although one patient developed unexplained jaundice.

The results of this investigation lend support to the concept that hypervolemia is a secondary rather than primary feature of the congestive state. It has been suggested[17, 18] that in subjects with congestive heart failure the blood volume expands as a direct consequence of the retention of sodium by the kidney; such a hypothesis implies that over short periods of time there occurs a selective expansion of the plasma volume during the congestive state with commensurate shrinkage as compensation is achieved. The results of this study fail to support this concept; instead, the red cell mass was found to be consistently and significantly increased, with variations in the degree of plasma volume expansion. Following treatment, selective shrinkage of the plasma volume was only rarely encountered. Expansion of the blood volume was

* Patients J.D., L.F., R.M., A.M., S.R., C.N.O., W.A.T., R.E.H., A.G.D.

† Patients J.D., L.F., R.M., A.M., S.R.

‡ Patients W.W.I., L.R.K., P.B., A.T., C.L.B., S.E.D., W.D., C.H.S., F.M.

apparently related to changes in the capacity of the "central reservoir," which includes the heart, the great vessels, and the pulmonary vascular tree. It is possible that expansion of this segment of the circulatory system "traps" sufficient blood to provide the stimulus for erythropoiesis. As the disorder progresses, there is further expansion of this "reservoir," as reflected by an increase in the size of the heart, eventuating in blood volume increments of considerable proportions. Digitalis may effectively reduce the size of the heart and, perhaps, the remainder of the central reservoir; this shrinkage in the vascular compartment is associated with a decrement in the volume of whole blood. On the other hand, when the heart size fails to decrease despite a prompt response to treatment, the volume of blood remains unchanged.

The results of this study, then, suggest that the primary factor leading to an increase in total blood volume is the stimulus for erythropoiesis caused by the expanded central reservoir, with plasma volume increasing in a secondary manner, rather than a primary expansion of plasma volume as a consequence of salt retention.

Conclusions

1. Total blood volume, red cell mass, and plasma volume have been determined with radiochromium-labeled red cells in 26 patients with congestive heart failure. The patients were categorized as *mild*, *moderate*, or *severe* according to the duration, severity, and tractability of the congestive process.

2. Measurements of blood volume, red cell mass, and plasma volume in subjects with congestive heart failure exceeded the values for a group of normal subjects by 22 per cent, 25 per cent, and 17 per cent.

3. In patients with *severe* congestive heart failure the measurements of blood volume exceeded those of the normal group by 38 per cent; in the *mild* group the values exceeded those of the normal group by only 14 per cent. The magnitude of the hypervolemia was correlated with the degree of cardiac enlargement but not with the increase in venous pressure, etiology of the heart disease, or quantity of edema fluid.

4. The circulating red cell mass was consistently expanded during the congestive state; selective expansion of the plasma volume was not encountered.

5. Following treatment, the blood volume decreased significantly in 50 per cent of the cases; shrinkage in blood volume occurred only in those subjects in whom the heart size decreased with treatment.

6. The quantity of edema fluid was not correlated with the expansion of plasma volume prior to treatment or the decrease in plasma volume following treatment.

Sumario Español

1. El volumen total de sangre, la masa total de eritrocitos y el volumen plasmático han sido determinados con células rotuladas con radiocromio en 26 pacientes en descompensación cardíaca. Los pacientes fueron catalogados como ligeros, moderados o severos de acuerdo a la duración, severidad y a la tratabilidad del proceso congestivo.

2. Determinaciones del volumen de sangre, masa de eritrocitos y volumen plasmático en sujetos con descompensación cardíaca excedieron los valores en un grupo de sujetos normales por 22 por ciento, 25 por ciento y 17 por ciento.

3. En los pacientes con descompensación cardíaca severa las determinaciones de volumen sanguíneo excedieron aquellas del grupo normal por 38 por ciento; en el grupo ligeramente descompensado los valores excedieron aquellos del grupo normal por 14 por ciento. La magnitud de la hipervolemia estuvo correlacionada con el grado de engrandecimiento cardíaco pero no con el incremento en presión venosa, etiología de la enfermedad cardíaca, o cantidad de fluído edematoso.

4. La cantidad circulante de masa de eritrocitos fué consistentemente expandida durante el estado de descompensación; expansión selectiva del volumen plasmático no fué encontrada.

5. Luego del tratamiento, el volumen sanguíneo disminuyó significativamente en 50 por

ciento de los casos; encogimiento en el volumen sanguíneo ocurrió solamente en aquellos sujetos en los cuáles el tamaño del corazón disminuyó con el tratamiento.

6. La cantidad de fluído edematoso no correlacionó con la expansión del volumen plasmático antes del tratamiento o al decremento en volumen plasmático después del tratamiento.

ACKNOWLEDGMENT

The author is indebted to Drs. Donald W. Seldin and Willis Sensenbach for their invaluable advice in the preparation of this paper.

Since this paper was submitted, two papers dealing with the same problem have appeared:

REILLY, WM. A., FRENCH, R. M., LAU, F. Y. K., SCOTT, K. G., AND WHITE, W. E.: Whole blood volume determined by radiochromium-tagged red cells. Circulation **9:** 571, 1954.

SCHREIBER, S. S., BOWMAN, A., YALOW, R. S., AND BERSON, S. A.: Blood volume alterations in congestive heart failure. J. Clin. Investigation **33:** 578, 1954.

REFERENCES

[1] GIBSON, J. G., 2ND, AND EVANS, W. A., JR.: Clinical studies of the blood volume. III. Changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure. J. Clin. Investigation **16:** 851, 1937.

[2] SEYMOUR, W. B., PRITCHARD, W. H., LONGLEY, L. P., AND HAYMAN, J. M., JR.: Cardiac output, blood and interstitial fluid volumes, total circulating serum protein, and kidney function during cardiac failure and after improvement. J. Clin. Investigation **21:** 229, 1942.

[3] MENEELY, G. R., AND KALTREIDER, N. L.: A study of volume of the blood in congestive heart failure. Relation to other measurements in 15 patients. J. Clin. Investigation **22:** 521, 1943.

[4] WALLER, J. V., BLUMGART, H. L., AND VOLK, M. C.: Studies of blood in congestive heart failure, with particular reference to reticulocytes, erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume. Arch. Int. Med. **66:** 1230, 1940.

[5] PETERS, J. P.: The role of sodium in the production of edema. New England J. Med. **239:** 353, 1948.

[6] ROSS, J. F., CHODOS, R. B., BAKER, W. H., AND FREIS, E. D.: The blood volume in congestive heart failure. Tr. A. Am. Physicians **65:** 75, 1952.

[7] CARDOZO, E. L.: The disappearance of the blue dye T-1824 from the blood stream into the thoracic duct lymph. Arch. neerl. physiol. **25:** 410, 1941.

[8] KING, B. G., COLE, K. S., AND OPPENHEIMER, E. T.: Disappearance curves of the dye T-1824 after its injection into the blood stream. Am. J. Physiol. **138:** 636, 1943.

[9] FERREBEE, J. W., LEIGH, O. C., AND BERLINER, R. W.: Passage of the blue dye T-1824 from the blood stream into the lymph. Proc. Soc. Exper. Biol. & Med. **46:** 549, 1941.

[10] WISH, L., FURTH, J., AND STOREY, R. H.: Direct determinations of plasma, cell and organ-blood volumes in normal and hypervolemic mice. Proc Soc. Exper. Biol. & Med. **74:** 644, 1950.

[11] NYLIN, G., AND HEDLUND, S.: Weight of the red blood corpuscles in heart failure determined with labeled erythrocytes during and after decompensation. Am. Heart J. **33:** 770, 1947.

[12] PRENTICE, T. C., BERLIN, N. I., HYDE, G. M., PARSONS, R. J., LAWRENCE, J. H., AND PORT, S.: Total red cell volume, plasma volume and sodium space in congestive heart failure. J Clin. Investigation **30:** 1471, 1951.

[13] HEDLUND, S.: Studies on erythropoiesis and total red cell volume in congestive heart failure. Acta med. scandinav. **146:** Suppl. 284, 1953.

[14] STERLING, K., AND GRAY, S. J.: Determination of circulating red cell volume in man by radioactive chromium. J. Clin. Investigation **29:** 1614, 1950.

[15] LANZ, H., MCCALL, M. S., AND SUTHERLAND, D. A.: An evaluation of a method using radiochromium tagged erythrocytes for the estimation of blood volume. To be published.

[16] CHAPLIN, H., JR., MOLLISON, P. L., AND VETTER, H.: The body/venous hematocrit ratio: Its constancy over a wide hematocrit range. J. Clin. Investigation **32:** 1309, 1953.

[17] MALLOY, H. T., AND EVELYN, K. A.: Determination of bilirubin with the photoelectric colorimeter. J. Biol. Chem. **119:** 481, 1937.

[18] WARREN, J. V., AND STEAD, E. A., JR.: Fluid dynamics in chronic congestive heart failure: An interpretation of the mechanisms producing the edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. Arch. Int. Med. **73:** 138, 1944.

[19] MERRILL, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: Evidence of forward failure as the primary cause of edema. J. Clin. Investigation **25:** 389, 1946.

The Effect of Acute Salt Loads on the Urinary Sodium Output of Normotensive and Hypertensive Patients before and after Surgery

By JESSE E. THOMPSON, M.D., THOMAS F. SILVA, M.D., DERA KINSEY, M.D., AND REGINALD H. SMITHWICK, M.D.

Under the stress of acute hypertonic salt loading, hypertensives excrete sodium at a much greater rate than normotensives. Immediately following splanchnicectomy, sodium excretion is markedly reduced in the hypertensive, but after several months it returns toward preoperative levels. There appears to be a rough correlation between maximum rate of sodium excretion and mean blood pressure. Normotensives by contrast exhibit insignificant differences pre- and postoperatively.

EVIDENCE from various sources indicates that the metabolism of sodium in patients with essential hypertension is probably different from that of normotensive patients. Perera and Blood[1] found that sodium restriction in normotensive control subjects was followed by a significant weight loss and increased urinary volume output, but these effects were not evident in hypertensive patients subjected to the same degree of sodium restriction. The sodium values in the urine, however, decreased to the same extent in both the normotensive and the hypertensive subjects. It is well known that hypertensives tolerate sodium restriction without difficulty and occasionally will exhibit a lowering of blood pressure. This is in marked contrast to the normotensive subject, who tolerates very poorly rigid sodium restriction. Our interest in this problem arises out of a long-term study of the effects of thoracolumbar splanchnicectomy on hypertensive cardiovascular disease in more than 2400 patients.[2] We have observed patients who fail to respond to a preoperative diet containing 200 mg. of sodium daily, who, following splanchnicectomy, respond with a lowering of blood pressure when a diet containing 1 Gm. of sodium daily is added to the postoperative regime. We have also observed in many instances that hypertensive patients postoperatively are unable to tolerate the strict regime of 200 mg. of sodium daily. The postsplanchnicectomy hypertensive patient thus appears to be more sensitive to sodium restriction than the unoperated one. We have numerous cases in which neither splanchnicectomy nor low-sodium diet alone was satisfactory in lowering blood pressure, but the combination of splanchnicectomy and moderate sodium restriction effected the desired result. Furthermore, there is some recent experimental evidence[3-7] which suggests that the sympathetic nerves may actually affect the handling of sodium by the kidney. On this background, therefore, we have studied the urinary output of sodium in normotensive and hypertensive patients subjected to acute sodium loads.

From the Departments of Surgery, Boston University School of Medicine and Massachusetts Memorial Hospitals, Boston, Mass.

Supported by a grant from the Trustees under the wills of Charles A. King and Marjorie King.

SUBJECTS AND METHODS

Acute salt loading tests were performed on eight hypertensive and five normotensive patients. Six of the hypertensives and four of the normotensives were tested before and immediately after surgery (one to two weeks). Three of the hypertensive patients were retested several months later. The hypertensives had bilateral splanchnicectomy performed, in which sympathetic ganglia D-8 to L-1 inclusive and the splanchnic nerves were removed. The normotensives had operations of comparable magnitude. All patients had normal renal and cardiac function. Salt and water intake was unrestricted in the days prior to the study except for the eight hours immediately prior to testing when the patients were thirsting and fasting. All tests were

done with subjects in the horizontal position. A catheter was placed in the bladder and urine collected during two 20-minute control periods. Approximately 500 cc. of 5 per cent sodium chloride was then infused intravenously over the course of one hour. Urine was collected at the end of the infusion and every 30 minutes thereafter for two additional hours. Blood samples for plasma sodium,

TABLE 1.—*Normotensives*

Pt.	Sex	Age	Operation	Time Relation to Operation	B.P.	Total Urine Volume (cc.)	Max. Urine Flow (cc./min.)	Total Urine Na % Load*	Max. Rate Na Excretion (mEq./min.)
1	F	43	Abdominal hysterec-	Pre	120/70	263	2.30	15.53	.568
F.S.			tomy	Post–7 d.		204	2.10	12.60	.535
2	M	31	Gastrectomy plus de-	Pre	130/85	458	3.76	21.66	.825
M.D.C.			hiscence	Post–16 d.	124/75	346	2.55	23.78	.758
3	M	47	Complicated recurrent	Pre	110/80	594	4.97	33.40	1.127
L.S.			herniorrhaphy	Post–7 d.		452	3.56	28.01	.892
4	M	29	Inguinal herniorrhaphy	Pre	100/60	458	4.50	22.51	.995
R.I.				Post–7 d.	102/50	648	5.00	32.25	1.050
5	F	30	Vaginal hysterectomy	Pre	126/72	433	3.30	19.65	.716
A.D.V.									

* The total urine sodium is calculated as the cumulative sodium output in mEq. from the beginning of loading to the end of the test, expressed as per cent of the total sodium load infused. (See figs. 1–4.)

TABLE 2.—*Hypertensives*

Pt.	Sex	Age	Operation	Time Relation to Operation	B.P.	Total Urine Volume (cc.)	Max. Urine Flow (cc./min.)	Total Urine Na % load	Max. Rate Na Excretion (mEq./min.)
1	M	45	Splanchnicectomy	Pre	176/98	1692	15.83	66.56	2.404
G.A.				Post–13 d.	142/76	573	4.00	34.68	1.086
				Post–3 mo.	140/77	1247	11.60	60.50	2.152
2	M	35	Splanchnicectomy	Pre	190/120	1135	8.87	55.00	1.743
K.W.				Post–12 d.	150/110	511	3.30	24.56	.735
				Post–9 mo.	140/95	726	6.76	33.00	1.394
3	M	50	Splanchnicectomy	Pre	165/105	852	6.47	44.86	1.300
B.G.				Post–14 d.	150/90	355	2.26	17.64	.501
				Post–3½ mo.	165/107	774	6.10	46.67	1.430
4	F	39	Splanchnicectomy	Pre	165/105	2036	17.25	82.23	3.107
L.D.				Post–13 d.	160/110	670	4.58	32.01	1.035
5	F	37	Splanchnicectomy	Pre	190/115	498	3.46	30.81	.893
B.D.				Post–14 d.	150/100	253	2.15	5.37	.256
6	M	37	Splanchnicectomy	Pre	186/124	1493	15.60	51.46	2.350
J.B.				Post–28 d.	176/117	888	7.83	38.69	1.629
7	F	42	Splanchnicectomy	Pre	230/130	1302	10.74	66.20	2.177
P.C.									
8	F	39	None	Pre	250/160	1530	13.83	62.48	2.530
C.L.									

TABLE 3.—*Mean Values*

	Total Urine Vol. (cc.)	Max. Urine Flow (cc./min.)	Total Urinary Na (% of infused load)	Max. Rate of Na Excretion (mEq./min.)
Normotensive—preop.	441.0	3.77	22.55	0.846
Normotensive-postop.	412.5	3.30	24.16	0.809
Hypertensive—preop.	1317.0	11.51	57.45	2.063
Hypertensive—immed. postop.....	542.0	4.02	25.49	0.874
Hypertensive—long-term postop.....	916.0	8.15	46.72	1.659

hemoglobin and hematocrit determinations were taken before the test, at the end of the infusion and at the end of the test. Urine volumes were recorded. The exact volume of the infusing solution was measured. Urine, plasma and infusate sodium determinations were done on the flame photometer. All blood pressure readings were taken in the horizontal position with a sphygmomanometer.

RESULTS

Table 1 lists the results obtained on the normotensive patients and table 2 the data on the hypertensives. Table 3 is a summary of the mean values. The average preoperative cumulative sodium output in the normotensives was 22.55 per cent of the infused load compared with 57.45 per cent in the preoperative hypertensives. The average maximum

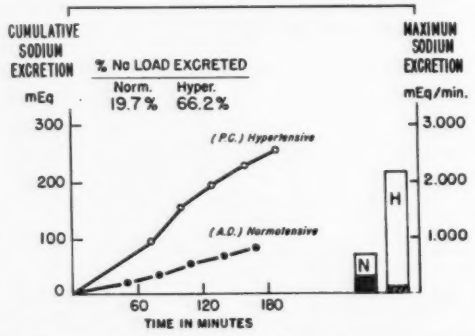


FIG. 1. Acute sodium loading in normotensive versus hypertensive subjects (unoperated). Note the greatly increased sodium excretion in the hypertensive under conditions of loading. The solid and the cross-hatched lower portions of the vertical bars represent the preloading control rates of sodium excretion. At basal rates the marked difference between normotensive and hypertensive was not apparent.

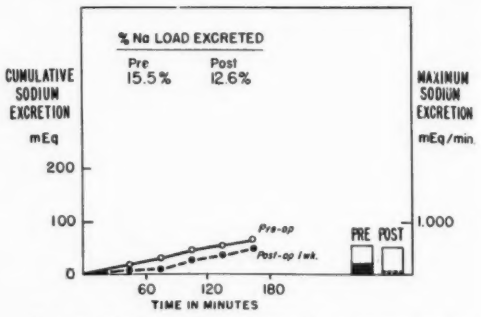


FIG. 2. Acute sodium loading in a normotensive subject (F. S.), pre- and postoperatively (hysterectomy). There was no significant difference in sodium excretion in this normotensive patient before and after total abdominal hysterectomy.

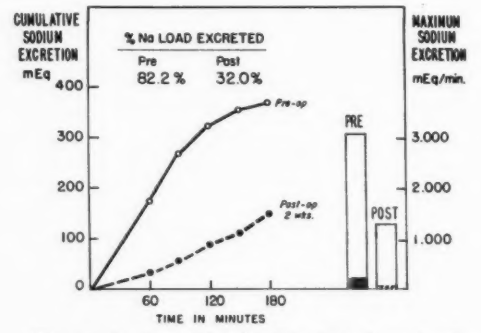


FIG. 3. Acute sodium loading in a hypertensive subject (L. D.), pre- and postoperatively (splanchnicectomy). Note the high level of sodium excretion in this hypertensive patient before operation and the marked depression 13 days following operation.

rate of sodium excretion in the preoperative normotensives was 0.846 mEq. per minute compared with 2.063 mEq. per minute in the preoperative hypertensives. Figure 1 compares normotensive patient A.D. with hypertensive patient P.C. in the unoperated state. The average postoperative cumulative sodium output in the normotensives was 24.16 per cent and the maximum rate of sodium excretion was 0.809 mEq. per minute. These are not materially different from the preoperative values. Figure 2 shows the pre- and postoperative data in normotensive patient F.S The average cumulative sodium output in the hypertensives immediately postoperative was 25.49 per cent and the average maximum rate

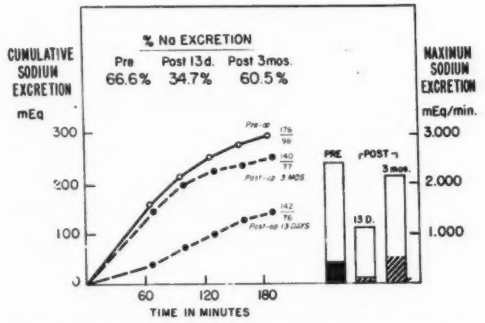


FIG. 4. Acute sodium loading in a hypertensive subject (G. A.), pre- and postoperatively (splanchnicectomy). At 3 months postoperative the sodium excretion was approaching the preoperative level and was considerably higher than the output at 13 days postoperative in spite of the fact that the blood pressure levels were the same at the two postoperative tests.

of sodium excretion was 0.874 mEq. per minute. This is a marked decrease from the preoperative levels in these patients. Figure 3 demonstrates the preoperative and the immediate postoperative data in hypertensive patient L.D. The average long-term postoperative cumulative sodium output in the hypertensives tested was 46.72 per cent, and the average maximum rate of sodium excretion was 1.659 mEq. per minute. These figures are considerably higher than those of the immediate postoperative period and approach the preoperative figures. Figure 4 shows these data plotted for hypertensive patient G. A. Also shown are the blood pressure data at the different levels of cumulative sodium excretion.

The average preoperative total urinary volume for the normotensives was 441 cc. for the test period and the maximum rate of urine flow was 3.77 cc. per minute, compared with an average for the hypertensives of 1317 cc. total volume and a maximum rate of 11.51 cc. per minute. The average postoperative urinary volume of the normotensives was 412.5 cc. and the average maximum rate 3.30 cc. per minute, values not appreciably different from the preoperative ones. The average urinary volume for the hypertensive patients immediately postoperative was 542 cc., and the average maximum rate was 4.02 cc. per minute. The average long-term postoperative volume for the hypertensives was 916 cc. and the maximum rate was 8.15 cc. per minute.

Figure 5 shows mean blood pressures plotted against maximum rates of sodium excretion.

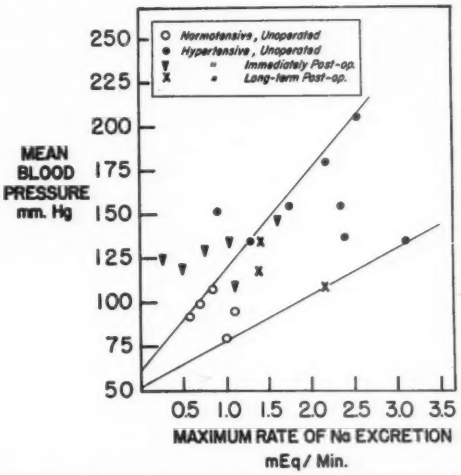


FIG. 5. Mean blood pressures plotted against maximum rates of sodium excretion. The mean blood pressure is calculated as half the sum of the systolic and diastolic levels. There is a rough correlation between the level of blood pressure and sodium excretion, except in the immediately postoperative hypertensive patients. These subjects exhibited lower rates of sodium output for a given blood pressure level.

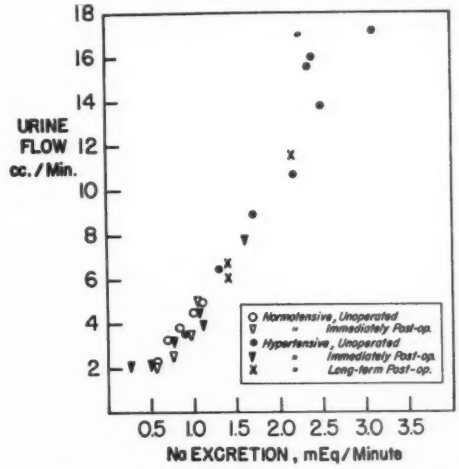


FIG. 6. Maximum rates of sodium excretion plotted against maximum rates of urine flow. Note the direct linear relationship regardless of the operative status of the patients.

There is a rough correlation between the level of blood pressure and sodium excretion, except in the immediately postoperative hypertensive patients. The latter subjects exhibited lower rates of sodium output for a given pressure level. Figure 6 is a graph of the maximum rates of sodium excretion plotted against the maximum rates of urine flow for all the subjects tested. The relationship is a direct linear one.

Increases in the plasma sodium concentration upon infusion of hypertonic saline were of the same order of magnitude in both the normotensive and hypertensive patients. The average peak value was in the vicinity of 150 mEq. per liter.

Discussion

A. Comparison of Hypertensives and Normotensives Unoperated. The studies reported here show that preoperative hypertensive patients reject a much higher proportion of infused sodium than do preoperative normotensives and excrete sodium at a greater rate under the stress of hypertonic salt loading. Our observations are in agreement with those of Farnsworth and Barker,[8] Weston and coworkers[9] and Birchall and associates.[10] The latter group also noted that a salt load was necessary to bring out the differences between normotensives and hypertensives, since they could not be distinguished on the basis of sodium excretion under reasonably basal conditions. Using mannitol diuresis, Brodsky and Graubarth[11] demonstrated the minute losses of sodium and chloride in the hypertensive to be two to two and one-half times greater than in the normal individual.

The reasons for the differences in sodium excretion in normotensives and hypertensives are not yet evident. Our own data are insufficient to determine whether the hypertensive filters more sodium or reabsorbs less of that presented to the tubules or both.

B. Comparison of Normotensives before and after Operation. The normotensive patient appears to have a very slightly but insignificantly lower rate of sodium excretion immediately following major surgery. One of the patients, however, actually had a slightly increased rate of sodium excretion postoperatively. The differences here are very small and are what one might expect on the basis of the metabolic response to the stress imposed by surgery.[12] The important point is that under the conditions of this study there was no appreciable difference in the pre- and postoperative rates of sodium output in the normotensives tested.

C. Comparison of Hypertensives before and after Splanchnicectomy. Our studies show that the hypertensive patient excretes a greatly reduced proportion of infused sodium at a greatly reduced rate two weeks following splanchnicectomy. When tested several months after splanchnicectomy the hypertensive excretes sodium at a slightly reduced rate or at the same rate when compared with the preoperative values.

The influence of splanchnicectomy, an operation which effects renal denervation, upon renal function and renal hemodynamics in man has not been completely elucidated. Pfeiffer and Wolff[13] have shown that renal hemodynamics may be altered in the direction of less vasoconstriction following operation. Wilkins and his collaborators,[14] however, have failed to demonstrate any change in the renal salt and water responses to venous congestion of the limbs after splanchnicectomy.

Freis and Smithwick[15] have noted an increase in the thiocyanate space of hypertensives in the second week after operation. They did not consider these changes a specific consequence of sympathectomy. If one reanalyzes the data of Freis and his coworkers,[15, 16] a very interesting fact is brought out. The average increase in "available fluid" volume of 12 hypertensives after splanchnicectomy was 17 per cent, with a range from +3 per cent to +28 per cent. By contrast, the average increase among eight normotensives after other operations was 3.6 per cent, with a range from −6 per cent to +8.5 per cent. This is further evidence that the hypertensive responds to the stress of surgery in a different fashion from the normotensive. Further investigations along these general lines might

be very rewarding. Whether splanchnicectomy has a specific effect or whether hypertensive patients subjected to an operation of comparable magnitude other than splanchnicectomy would show similar salt and water responses must still be determined.

There are in the literature several recent reports on the effects of splanchnic nerve resection upon renal electrolyte excretion. It has been reported in acute experiments on anesthetized normotensive dogs that renal denervation may result in an increased elimination of sodium, chloride, and water, with and without increases in the glomerular filtration rate.[3-6] In the unanesthetized, chronically denervated dog, Surtshin and associates[7] have demonstrated equal excretion of water and sodium from the denervated and control kidneys. Ether and pentobarbital anesthesia, however, produced falls in water and sodium excretion in the normal kidney but not in the denervated one. Similar results, when autonomic blocking drugs are used, have also been reported.[17-19] It is entirely possible that the effects of splanchnicectomy on the kidney are brought out only under specific conditions of stimulation. This may be the state of affairs in the human, where splanchnicectomy is known to abolish certain normally active splanchnic bed vasoconstrictor reflexes.

D. Comparison of Blood Pressure Levels with Rates of Sodium Excretion. Figure 5 is a graph of mean blood pressure plotted against maximum rate of sodium excretion. In a general way the rate of sodium excretion is proportional to the mean blood pressure level. The correlation is not too strict and may be representative of the variability which blood pressure is known to exhibit. Green and coworkers[20] have reported a fairly strict correlation between the level of the mean blood pressure and the rate of sodium excretion.

It is of interest to note that the immediately postoperative hypertensive patients tend to fall above the others on the graph; that is, at the same level of blood pressure the rate of sodium excretion is lower. All of this lends further support to the primary thesis that the metabolism of sodium is somehow involved in the basic mechanism of hypertensive disease.

E. Comparison of Rates of Urine Output and Rates of Sodium Excretion during Salt Loads. Figure 6 depicts a graph of rate of urine flow plotted against maximum rate of sodium excretion. It is evident that this is a direct linear function and confirms the finding of Weston and colleagues[9] that there is a direct proportionality between the urine volume and the rate of electrolyte excretion in hypertensive patients. This curve is characteristic of an osmotic diuresis. Our normotensive data appear to fall along the same line as the hypertensive. Also, the immediately postoperative data and the long-term postoperative data appear to fall along the same line. It appears, therefore, that whatever mechanism is responsible for the marked decrease in sodium excretion in the hypertensive patient immediately after operation is equally effective in reducing the water output by the kidneys, under the conditions of these studies. In our experiments splanchnicectomy appears to have no differential influence upon the rate of sodium excretion when compared with the rate of urine flow. From the data we can make no statement relative to the long-term effects of splanchnicectomy upon the rate of sodium excretion which might explain the apparent sensitivity to salt restriction which the postoperative patients exhibit. Further investigations are necessary.

Summary

1. In acute salt-loading tests it has been observed that preoperative hypertensive patients reject a much higher proportion of infused sodium than do preoperative normotensive patients.

2. The normotensives have an insignificantly lower rate of sodium excretion immediately following major surgery. The hypertensives excrete a greatly reduced proportion of infused sodium at a greatly reduced rate immediately following splanchnicectomy.

3. The hypertensive patients tested several months after splanchnicectomy excrete sodium

at a slightly reduced rate or at the same rate as before operation.

4. There is a direct relationship between the rate of sodium excretion and the rate of urine flow during the stress of acute salt loading in both normotensives and hypertensives before and after operation.

5. There appears to be a rough correlation between the maximum rates of sodium excretion and the levels of mean blood pressure in both normotensives and hypertensives, except in the immediate period after splanchnicectomy in the hypertensive group when the rate of sodium excretion is reduced even at high blood pressure levels.

Sumario Español

1. En pruebas de recarga aguda con sal se ha observado que los pacientes preoperatorios hipertensos rechazan una proporción mucho mayor del sodio instilado que los pacientes preoperatorios normotensos.

2. Los normotensos tienen un promedio insignificativamente más bajo de excreción de sodio inmediatamente después de cirugía mayor. Los hipertensos eliminan una proporción, grandemente reducida del sodio instilado a una velocidad grandemente reducida inmediatamente después de la esplacnicocectomía.

3. Los pacientes hipertensos probados algunos meses después de la esplacnicocectomía eliminan sodio a una velocidad ligeramente reducida o a la misma velocidad que antes de la operación.

4. Hay una relacción directa entre la velocidad de excreción del sodio y la velocidad de producción de orina durante el esfuerzo de la recarga aguda con sal en ambos normotensos e hipertensos antes y después de la operación.

5. Aparenta haber una correlación tosca entre la velocidad máxima de excreción de sodio y los niveles de presión arterial promedio en ambos normotensos e hipertensos, excepto en el período inmediato después de la esplacnicocectomía en el grupo hipertenso cuando la velocidad de excreción del sodio se reduce, aùn a niveles altos de presión arterial.

References

[1] Perera, G. A., and Blood, D. W.: Disturbance in salt and water metabolism in hypertension. Am. J. Med. **1:** 602, 1946.

[2] Smithwick, R. H., and Thompson, J. E.: Splanchnicectomy for essential hypertension. J. A. M. A. **152:** 1501, 1953.

[3] Kaplan, S. A., Fomon, S. J., and Rapoport, S.: Effect of splanchnic nerve division on urinary excretion of electrolytes during mannitol loading in the hydropenic dog. Am. J. Physiol. **166:** 641, 1951.

[4] —, and Rapoport, S.: Urinary excretion of sodium and chloride after splanchnicectomy; effect on the proximal tubule. Am. J. Physiol. **164:** 175, 1951.

[5] Kriss, J. P., Futcher, P. H., and Goldman, M. L.: Unilateral adrenalectomy, unilateral splanchnic nerve resection and homolateral renal function. Am. J. Physiol. **154:** 220, 1948.

[6] Sartorius, O. W., and Burlington, H.: Effects of denervation on renal function in the dog. Federation Proc. **11:** 137, 1952.

[7] Surtshin, A., Mueller, C. B., and White, H. L.: Effect of acute changes in glomerular filtration rate on water and electrolyte excretion. Federation Proc. **11:** 157, 1952.

[8] Farnsworth, E. B., and Barker, M. H.: Tubular resorption of chloride in hypertensive and in normal individuals. Proc. Soc. Exper. Biol. & Med. **52:** 74, 1943.

[9] Weston, R. E., Hellman, L., Escher, D. J. W., Edelman, I. S., Grossman, J., and Leiter, L.: Studies on the influence of the low sodium cardiac diet and the Kempner regimen on renal hemodynamics and electrolyte excretion in hypertensive subjects. J. Clin. Investigation **29:** 639, 1950.

[10] Birchall, R., Tuthill, S. W., Jacobs, W. S., Trautman, W. J., Jr., and Findley, T.: Renal excretion of water, sodium. and chloride. Circulation **7:** 258, 1953.

[11] Brodsky, W. A., and Graubarth, H. N.: Excretion of water and electrolytes in patients with essential hypertension. J. Lab. & Clin. Med. **41:** 43, 1953.

[12] Moore, F. D., and Ball, M.: The metabolic response to surgery. Springfield, Ill., Charles C Thomas, 1952.

[13] Pfeiffer, J. B., Jr., and Wolff, H. G.: Studies in renal circulation during periods of life stress and accompanying emotional reactions in subjects with and without essential hypertension. Observations on role of neural activities in regulation of renal blood flow. J. Clin. Investigation **29:** 1227, 1950.

[14] Wilkins, R. W., Tinsley, C. M., Culbertson, J. W., Burrows, B. A., Judson, W. E., and

BURNETT, C. H.: The effects of venous congestion of the limbs upon renal clearances and the excretion of water and salt. J. Clin. Investigation **32:** 1101, 1953.

[15] FREIS, E. D., AND SMITHWICK, R. H.: The effect of lumbodorsal splanchnicectomy on the blood volume and "thiocyanate space" of patients with essential hypertension. Am. J. M. Sc. **214:** 363, 1947.

[16] LYON, R. P., STANTON, J. R., FREIS, E. D., AND SMITHWICK, R. H.: Blood and "available fluid" (thiocyanate) volume studies in surgical patients. Surg., Gynec. & Obst. **89:** 9, 1949.

[17] BLAKE, W. D.: Some effects of dihydrogenated ergot alkaloids on renal hemodynamics, water and electrolyte excretion in the dog. Am. J. Physiol. **173:** 337, 1953.

[18] BOYLAN, J. W., GENEWICH, J., AND ANTKOWIAK, D.: Absorption and excretion of water and salt following autonomic blockade (TEAC) in the dog: chronic renal denervation. Am. J. Physiol. **173:** 151, 1953.

[19] MOYER, J. H., AND MILLS, L. C.: Hexamethonium —its effect on glomerular filtration rate, maximal tubular function, and renal excretion of electrolytes. J. Clin. Investigation **32:** 172, 1953.

[20] GREEN, D. M., WEDELL, H. G., WALD, M. H., AND LEARNED, B.: The relation of water and sodium excretion to blood pressure in human subjects. Circulation **6:** 919, 1952.

CLINICAL PROGRESS

EDITOR: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Errors in the Recognition and Treatment of Heart Disease

By R. BRUCE LOGUE, M.D., AND J. WILLIS HURST, M.D.

THE medical literature is replete with communications on heart disease. Despite this abundant literature, errors are made in recognizing and treating diseases of the heart. This report describes some of the more common errors encountered in practice and offers certain clues that may be helpful in preventing some of the mistakes.

CHEST PAIN

The diagnosis of angina pectoris is established by the presence of a characteristic history and does not depend upon the presence of electrocardiographic abnormalities. The pain is usually substernal and occurs characteristically during effort, emotional stress, exposure to cold or after a large meal. It is not well appreciated that it may occur on assuming the recumbent position. The duration is one to five minutes as a rule and relief may be prompt with rest or the administration of nitroglycerin. In inquiring regarding angina, it is not sufficient to ask about pain alone. Since pain may be denied, one should therefore ask about indigestion, tightness, squeezing, burning, heaviness or choking. Discomfort may occur in the arms, epigastrium, back or jaw without being present in the anterior chest. While precordial pain is rare in angina pectoris, it may occur. The sudden onset of angina for the first time or the change in its frequency or severity usually signifies coronary occlusion and rarely myocardial infarction. Judicious periods of rest when such changes occur may allow collateral circulation to develop and forestall infarction. In the elderly sedentary patient, discomfort may occur only after meals and one should be suspicious of "indigestion" accompanied by sweating or weakness. Many patients have prolonged pain without accompanying evidence of myocardial necrosis such as persistent electrocardiographic changes, fever, leukocytosis and an elevated sedimentation rate. These patients require sharp reduction in physical and mental activity and should be treated much like the patient with infarction, though with more freedom about the room and with shorter periods of rest. There is still a reluctance to make a clinical diagnosis of myocardial infarction without a drop in blood pressure or pulmonary rales, even with prolonged pain. It seems hardly necessary to emphasize that infarction often occurs without any changes on physical examination, and without leukocytosis, fever or elevation of the sedimentation rate.

The pain associated with emotional tension may be confused with coronary disease. While the precordial and inframammary location of the sharp, sticking or lancinating pain and accompanying hyperesthesia is well known, it is not widely known that precordial oppression or dull aching may occur. This is differentiated from coronary disease by the fact that it may last for hours or days, is unrelated to effort and unrelieved by nitroglycerin. It is frequently accompanied by the hyperventilation syndrome. There may be sighing respiration, weakness, giddiness, palpitation and heart consciousness. This pain is more often unrelated to heart disease, but at times is the disabling symptom

From the Department of Medicine, Emory University School of Medicine, Emory University Hospital, Emory, Ga.

due to anxiety accompanying organic heart disease.

We should not neglect to determine whether pain is aggravated by deep breathing, turning, coughing or swallowing, for this suggests pericarditis. The sudden onset of such pain accompanied by the early presence of a pericardial friction rub and fever may indicate acute benign pericarditis, a condition which is often misdiagnosed myocardial infarction.

Patients with pulmonary hypertension may experience pain indistinguishable from that of coronary disease.[1] It is usually accompanied by dyspnea and occasionally by cyanosis. Nitroglycerin may give no relief, but intravenous aminophylline may be followed by dramatic improvement. Asthma, emphysema, mitral stenosis and interatrial defect are the more common causes of pulmonary hypertension. A history of repeated attacks of "coronary occlusion" in such a patient should arouse suspicion of pulmonary hypertensive pain.

The pain of gall bladder disease may closely simulate that of coronary disease. Intermittent, epigastric or lower substernal cramping pain unrelated to effort, particularly when associated with nausea, chilliness, or back pain suggests gall bladder disease.

Degeneration of a cervical disc may produce pain in the shoulder, arm and upper chest. The occurrence of prolonged numbness and paresthesias in the arms and hands without relation to exertion but with aggravation on lateral flexion or hyperextension of the head suggests the diagnosis. Tenderness on palpation over the course of the nerve trunks at their exit is common.

The pain of dissecting aneurysm may be mistaken for myocardial infarction. Clues of dissecting aneurysm which may be overlooked are tearing chest pain with persistence of hypertension, the development of aortic insufficiency, pulse or blood pressure differences between the arteries of the neck, upper extremities or lower extremities, pulsation of a sternoclavicular joint, or chest pain accompanied by transient paralysis of the legs.

One should resist the temptation to ascribe substernal discomfort to the presence of an hiatal hernia so commonly demonstrated by x-ray examination since these are rarely responsible for pain. Furthermore, the experienced radiologist may at times be unable to distinguish a phrenic ampulla from an hiatal hernia. Pain due to "esophageal spasm" may be misinterpreted as angina. It is intermittent, spasmotic, unrelated to effort and is prone to occur under emotional tension and after dietary indiscretion. The pain of the "splenic flexure syndrome" is never substernal but is localized to the inframammary or precordial region and may be referred to the left arm. It may be exactly reproduced by distending the splenic flexure through a tube, and relief may be obtained following an enema.

Congestive Heart Failure

There is a widespread tendency to diagnose congestive heart failure without establishing the etiology. The common causes of heart disease leading to congestive failure are coronary arteriosclerosis, hypertension, rheumatic heart disease and congenital heart disease. In the absence of characteristic findings of these usual diseases, one should ask: (1) Are the symptoms and findings due to heart failure? (2) Is there pericardial or diffuse myocardial disease? (3) Is there an extracardiac cause of circulatory overloading such as acute nephritis or peripheral arteriovenous fistula? After establishing the etiologic type of heart disease, one should routinely search for a precipitating cause of the heart failure. This is of prime importance since success of therapy may depend on control of the precipitating factor. Infections, particularly respiratory, are the most common initiating and aggravating factors in congestive heart failure. Pulmonary embolism, acute rheumatic fever, acute myocardial infarction, cardiac arrhythmia, overloading with fluid and salt, bacterial endocarditis, thyrotoxicosis, hormone therapy, liver disease, renal disease and urinary retention are other important sources of aggravation. The presence of fever may be a clue to some of these since fever of more than 2 degrees does not occur with uncomplicated heart failure.[2]

Congestive heart failure is often unrecognized in spite of a characteristic history of paroxysmal nocturnal dyspnea, since there may be no rales

in the lungs several hours after such an episode. On the other hand, nocturnal hyperventilation due to anxiety may be misdiagnosed as congestive heart failure. It is not sufficiently recognized that hyperventilation may awaken a person from sound sleep. Ancillary symptoms suggesting hyperventilation are numbness and tingling of the lips, face or hands, giddiness or blacking out sensations, feeling of impending doom and chest oppression. Sighing respiration with inability to get a satisfying breath is a common manifestation between attacks. The hyperventilation syndrome is not uncommon in the person with organic heart disease.

It is often difficult to determine whether dyspnea is due to cardiac or pulmonary disease. The wheezing of bronchial and cardiac asthma may be indistinguishable. Each may be aggravated by effort and occur at night. Asthma appearing initially in middle life should be considered as a manifestation of heart failure until proven otherwise. The response to epinephrine and aminophylline do not differentiate the two conditions. The dyspnea resulting from bronchial asthma, emphysema, pulmonary fibrosis, and chronic pulmonary infection may be misinterpreted as heart failure. Whenever there is no clinical evidence of coronary, hypertensive or valvular heart disease and the heart size is normal, one should suspect a pulmonary origin of dyspnea and wheezing. At times, one must resort to a therapeutic trial of mercurial diuretics, digitalis and salt restriction to determine whether dyspnea is due to heart failure or to pulmonary disease. A weight loss of 4 pounds within 24 hours following a mercurial diuretic suggests congestive heart failure in the absence of renal or hepatic disease.[3] This approach is particularly important where heart and lung disease coexist. In the management of patients with chronic lung disease, one should not neglect the use of antibiotics and bronchodilators.

One should not overlook the importance of anemia, obesity, thyrotoxicosis and metabolic acidosis as the sole cause or as an aggravating factor of dyspnea. It is not well appreciated that dyspnea is a frequent complaint in constrictive pericarditis and significant pericardial effusion.

Edema is a late manifestation of heart failure. It should be recalled that 10 to 15 pounds of extracellular fluid may accumulate without pitting edema. Edema of the extremities may be due to obesity, varicose veins, old or recent phlebitis, cirrhosis of the liver, nephritis, or hypoproteinemia, and may be misinterpreted as evidence of congestive heart failure. Less common causes of edema such as lymphedema, myxedema, hormone imbalance due to menstruation, pregnancy and the menopause, and hormone therapy may be encountered. The edema of heart failure accumulates in the most dependent portions of the body. Thus one should not neglect to examine the presacral region of the bedridden patient. Another factor which determines the location of edema is tissue pressure. Such pressure may be low in the periorbital region, particularly in children, and the edema that occurs in this area may simulate renal disease. From a practical standpoint, one may exclude heart failure as a cause of edema if the heart size is normal by x-ray examination. Two possible exceptions to this rule are cor pulmonale and constrictive pericarditis.

There may be no liver enlargement in the adult with mild congestive heart failure, and ascites is a late manifestation. One exception is constrictive pericarditis which is characterized by the early appearance of liver enlargement and ascites. When ascites is due to congestive heart failure, the liver is invariably enlarged as contrasted to Laennec cirrhosis in which the liver may or may not be enlarged. Gaseous distension is a frequent complaint in association with hepatomegaly. Acute tenderness on palpation of the liver area suggests that enlargement has been rapid in development and of recent origin. Although liver engorgement may produce discomfort, one should not overlook peptic ulcer or other gastrointestinal disease as a cause of pain. Chronic cough or insomnia due to Cheyne-Stokes respiration may be predominant symptoms due to congestive heart failure and their significance may be overlooked.

There are certain physical signs particularly useful in the evaluation of the failing heart. Diastolic gallop rhythm is a frequent finding in the presence of myocardial insufficiency and

should be differentiated from the unimportant systolic gallop rhythm. At times a diastolic gallop can be better seen or palpated rather than heard. Pulsus alternans is another indication of myocardial insufficiency; it is commonly overlooked since sufficient care is not taken in determining the systolic pressure. Exercise may be necessary to bring out both diastolic gallop rhythm and pulsus alternans. The significance of pulmonary rales due to congestive heart failure is well known; however, it should be recalled that interstitial pulmonary congestion may be present without rales. In such cases x-ray study of the chest may reveal pulmonary congestion; this may prevent the unwary from making an erroneous diagnosis of the hyperventilation syndrome. One should remember that rales may be due to causes other than heart failure such as chronic lung disease, hypostasis, pneumonia, atelectasis, aspiration, or to pulmonary embolism.

A careful study of the neck veins is often neglected. Although neck vein distension is common in congestive heart failure, pulmonary congestion may occur without obvious venous engorgement. The deep systolic jugular venous pulsation is usually misinterpreted as an arterial pulsation, and its significance is missed. The usual cause of such pulsation is relative tricuspid insufficiency resulting from chronic congestive heart failure. It is less commonly due to organic tricuspid insufficiency. This finding is important because in a large percentage of cases there may be no accompanying tricuspid murmur. One must find the optimum semirecumbent position in order to observe the systolic pulsation of the deep jugular veins. Light compression obliterates such a venous pulsation without altering the underlying arterial pulsation; furthermore, hepatic compression accentuates the venous overfilling.

Heart failure will be overlooked in children if one expects the manifestations usually seen in the adult. For example, there may be few rales in the dyspneic child, the liver enlarges quite early, and there may be minimal peripheral edema, even when ascites is present. The occurrence of periorbital edema may cause confusion with nephritis. Tachypnea is a more prominent feature than in the adult and is commonly attributed to pneumonia. Congestive heart failure is commonly precipitated by respiratory infection in the child with heart disease. Therapy should be directed towards treatment of both the infection and the heart failure.[4]

When heart failure ceases to respond in the expected manner to adequate therapy, it is natural to assume that there is progressive deterioration of cardiac function. However, one should again consider certain extracardiac factors which may be responsible. Such things as electrolyte depletion, acute myocarditis, pulmonary embolism, pulmonary infection, thyrotoxicosis, renal and liver disease, and digitalis intoxication may be responsible.

Cardiac Arrhythmias

Paroxysmal auricular tachycardia is often unrecognized in spite of a characteristic history of sudden onset and cessation of rapid heart beat. The attack may be terminated by carotid sinus pressure in about one-third of the patients; however, this procedure is often overlooked or improperly performed. Carotid sinus pressure during the recording of an electrocardiogram may serve to identify the occasional case of sinus tachycardia simulating auricular tachycardia. The treatment of choice in the patient who does not respond to simple measures producing vagal stimulation is the administration of a rapidly acting digitalis preparation.[5] Transient cardiac standstill or short runs of ventricular tachycardia are probably not uncommon at the termination of an attack, regardless of the type of therapy, and this does not preclude digitalis therapy for subsequent attacks. Simple sedation should not be overlooked in addition to the above measures.

Auricular fibrillation often occurs in the absence of demonstrable heart disease. Mitral stenosis, coronary disease and thyrotoxicosis are the commonly recognized organic causes of this arrhythmia. Less common causes which may be overlooked are pulmonary embolism, pulmonary infection, bronchial obstruction with atelectasis, constrictive pericarditis, acute pericarditis, digitalis intoxication, potassium depletion, active rheumatic fever, anesthesia, hypoxia and interatrial septal defect. There is

usually no problem in recognizing paroxysmal auricular fibrillation; however, aberration of the QRS complexes of the electrocardiogram may simulate ventricular tachycardia. The management is frequently improper. It is often forgotten that the aim of initial therapy is to slow the uncontrolled ventricular rate as rapidly as possible, and this can best be accomplished by rapid digitalization. Furthermore, paroxysmal auricular fibrillation is frequently reverted to sinus rhythm following such therapy, particularly when there is no demonstrable heart disease. When auricular fibrillation persists, quinidine can then be given. Despite the wave of enthusiasm for conversion of all cases of chronic auricular fibrillation, our personal experience justifies a word of warning. Such therapy is not without the small and unpredictable risk of major embolic episodes or sudden death, presumably due to ventricular fibrillation.

Auricular flutter is usually associated with organic heart disease; it is more disturbing to the patient because of wide variations in rate occasioned by variable A-V block, and is more resistant to therapy. The treatment of choice is the cautious administration of digitalis to full therapeutic levels. This produces slowing of the ventricular rate by increasing A-V block or by causing auricular fibrillation which may subsequently revert spontaneously to sinus rhythm. Quinidine may be useful in those who do not respond to digitalis, but such therapy is less often successful than in cases of auricular fibrillation.

Ventricular tachycardia may be confused with auricular tachycardia with bundle-branch block or aberrant conduction and at times differentiation may be impossible. The rate may vary slightly over a period of time but does not respond to carotid sinus pressure. The use of an esophageal lead often serves to identify the rhythm by demonstrating independent auricular and ventricular rhythms. When the rhythm cannot be definitely identified as supraventricular, it should be treated as ventricular tachycardia with quinidine or procaine amide. It is important to remember that the drugs used in treating ventricular tachycardia may also produce this rhythm in toxic doses.

Syncope

While syncope is not a common symptom of heart disease, it may be a disturbing complaint, and when accompanied by convulsions may be mistaken for epilepsy. Stokes-Adams attacks are one of the more important causes of transient unconsciousness. They are more often associated with coronary disease but are not uncommon in the presence of aortic stenosis. It should be remembered that episodes may occur with a normal electrocardiogram and normal P-R interval between attacks. While the majority of attacks are due to cardiac standstill, they may be due to ventricular tachycardia or to ventricular fibrillation. Syncope may occur during exertion in the patient with advanced aortic regurgitation or with aortic stenosis. Excessive ventricular rates during paroxysmal tachycardia or the transient standstill at the end of an attack may be responsible for unconsciousness. The onset of a cerebrovascular accident may be confused with syncope of cardiac origin. Points of help in differentiation are: flushing, slow stertorous respiration, preceding symptoms such as headache, weakness or paresthesias of the lips or extremity, neurologic signs, or loss of memory for recent events. It is now apparent that thrombosis of an atherosclerotic carotid artery is a common cause of cerebral vascular accident with or without associated syncope. Other causes of syncope which should not be neglected are: hyperirritable carotid sinus reflex, emotionally induced vasovagal attacks, postural hypotension, cough syncope, spontaneous hypoglycemia, hyperventilation syndrome, pulmonary embolism, dissecting aneurysm and epilepsy.

Rheumatic Heart Disease

Rheumatic fever in early childhood manifests itself largely in the form of carditis and not polyarthritis; it may be readily overlooked. Rheumatic fever is more common in the age group between 5 and 15, but it is an error to assume that it does not occur at an earlier age.[5] The first suspicion of the disease may be aroused by the development of a systolic murmur at the apex in the child with a history of repeated sore throats. While joint symptoms

may be present in about half of all children, they may be vague and indefinite. Rheumatic fever is the most common cause of heart failure in childhood, and under such circumstances a significant systolic murmur is present at the apex. The predominant apical location of murmurs serves to differentiate rheumatic from congenital lesions in which the murmurs are largely basal or midsternal in location. It is often assumed that a diastolic rumble at the apex indicates mitral stenosis; however, such a murmur is not uncommon in acute rheumatic fever and it may disappear as activity subsides. It should be recalled that a diastolic apical rumble may also occur with such congenital lesions as patent ductus arteriosus or large ventricular or atrial septal defects. Recent experience indicates that the majority of patients thought to have Lutembacher's syndrome have only an interatrial septal defect.[6] An error is made in assuming that rheumatic fever is inactive when the sedimentation rate is normal, since a normal rate may occur in the presence of congestive heart failure. Contrary to prevailing impression, a single electrocardiogram is of limited usefulness in the recognition of rheumatic fever. In addition to first degree A-V block, nodal rhythm and interference dissociation may occur in acute rheumatic fever. It should not be forgotten that a number of the common childhood diseases may produce a prolonged P-R interval. Despite the adequate evidence that the recurrence of rheumatic fever may be significantly diminished by long-term prophylaxis with penicillin and sulfa drugs, this type of therapy is being constantly neglected. Every effort should be made to treat pharyngitis or sore throat in the rheumatic subject promptly with the appropriate chemotherapy. The common error is the failure to continue chemotherapy for at least 7 to 10 days in order to eradicate the streptococci.[7] Furthermore, the rheumatic subject should be protected by adequate chemotherapy while hospitalized on an open ward, since the frequency of respiratory infection is so great. It is a mistake to expect cure of rheumatic fever from the administration of cortisone or corticotropin (ACTH) since available evidence lends no support for such a view. It is apparent that the hormones do not prevent the development of valvular damage and their chief usefulness lies in tiding the patient over a critical period.

The murmur of mitral stenosis may be missed unless the patient is examined in the left lateral position after exercise with the bell of the stethoscope. At times a split or reduplicated mitral first sound may be misinterpreted as a presystolic murmur. The absence of a mid-diastolic rumble in such a case virtually eliminates the possibility of mitral stenosis. The murmur of mitral stenosis may be obscured by paroxysmal auricular tachycardia, auricular fibrillation or pulmonary edema and it is important to re-examine the patient after these have been corrected. With the advent of mitral commissurotomy, it has become apparent that the murmur of tricuspid insufficiency may be transmitted towards the apex and be confused as the murmur of mitral insufficiency. In the patient with mitral stenosis, it may be impossible to differentiate the murmur of aortic insufficiency from the murmur of relative pulmonary insufficiency, although when the intensity of the murmur varies from time to time the latter lesion is more likely.

The most common valvular heart disease after age 50 is calcific aortic stenosis. It is missed with surprising regularity. The murmur is usually heard in the aortic area and is transmitted to the neck. The murmur is often attributed to dilatation of the aorta due to atherosclerosis or hypertension. It may be obscured or heard only in the neck in the presence of emphysema. It may diminish during acute heart failure, shock or during cardiac arrhythmia. The murmur is rough in quality but need not be loud. A thrill is present in about one-third of the cases.[8] The murmur may be heard with maximum intensity at the apex or to the left of the sternum for years before it is recognized as arising at the aortic area. When the murmur is heard at the precordial region it may have a musical quality. The aortic second sound is normal in approximately half of all cases, and a small pulse pressure is a very late and infrequent sign. A marked degree of left ventricular hypertrophy with strain pattern in the electrocardiogram in the absence of hypertension should lead one to suspect aortic

stenosis. Unfortunately, many diagnoses are missed because a careful search for aortic valve calcification is neglected; however, the absence of calcification does not exclude the lesion. The association of angina pectoris and syncope demands a careful search for aortic stenosis. Unexplained fever in the elderly is occasionally found to be due to bacterial endocarditis superimposed on the aortic valve.

Bacterial Endocarditis

The commonly expected findings of petechiae, splenomegaly, hematuria and leukocytosis occur in less than one-half of cases of bacterial endocarditis.[9] Unexplained fever of a week's duration is sufficient grounds for strongly suspecting bacterial endocarditis in the patient with valvular or congenital heart disease and demands blood cultures. On the other hand, an occasional case of bacterial endocarditis has been observed in which there was no fever. An uncommon presenting manifestation of bacterial endocarditis is anemia.[10]

The prior administration of antibiotics may produce bacteriostasis, and positive blood cultures may be obtained with difficulty. Sensitivity tests are useful in determining the relative resistance of organisms but the conventional tests measure bacteriostatic, not bactericidal, effect. Thus one may be misled by a report of marked sensitivity in vitro and yet the in vivo effect may be inadequate for cure. There is a general tendency to use inadequate dosage which may hasten the emergence of resistant strains. It is probably unwise to use less than 10 million units penicillin daily initially while awaiting positive cultures or the results of sensitivity tests. The concomitant use of streptomycin is indicated, irrespective of the sensitivity of the organism.[11] The alarming frequency of infections due to resistant strains of staphylococci is noteworthy, and such cases may require extremely large doses of penicillin for cure (60–100 million units) or the simultaneous use of several antibiotics including erythromycin.

Congenital Heart Disease

Space will not permit a detailed discussion of the common errors made in each of the numerous types of congenital heart disease. Therefore, only a few of the common mistakes are enumerated.

The parent's history regarding cyanosis at birth may be misleading. Mild degrees of arterial oxygen unsaturation may be overlooked and with the passage of time more obvious cyanosis may be apparent. For example, an infant with tetralogy of Fallot may not appear cyanotic at birth, and persistent cyanosis may not be noted until after several months. All cyanosis is not due to congenital heart disease but may be due to chronic lung disease or pulmonary arteriovenous fistula. There is still much confusion regarding the proper interpretation of murmurs. The mere presence of a murmur does not necessarily indicate heart disease. Indeed slight murmurs may be heard in most perfectly normal children. If one hears a murmur which is definitely abnormal, the physician may be able to state that heart disease is present but should not forget that many different defects can produce similar murmurs. For example, a similar basal systolic murmur may be produced by patent ductus, pulmonic stenosis, interatrial septal defect and interventricular septal defect. The absence of murmurs does not rule out congenital heart disease. For instance, endocardial fibrosis, tricuspid atresia, interatrial septal defect, and pulmonary atresia at times may be present without murmurs. In the very young, it may be difficult to localize a murmur because in the thin, small chest, murmurs may be widely transmitted.

The murmur of patent ductus may be heard only in systole during the first few years of life, and it may be impossible to differentiate it from a normal murmur. At an increased age the murmur of patent ductus is usually continuous, but one must not forget that there are other causes of continuous murmurs. The most common continuous murmur is due to a normal venous hum, and abnormal continuous murmurs can be heard in aortic septal defect, pulmonary A-V fistula, collateral circulation in truncus arteriosus or pseudotruncus and anomalous pulmonary venous drainage. A diastolic rumble at the apex may be heard in patients with patent ductus arteriosus, interatrial and interventricular septal defect. One of

the difficulties in the recognition of coarctation is the difficulty of obtaining the blood pressure or pulses in the normal newborn. Patients with pure pulmonic stenosis are not cyanotic, contrary to a widespread erroneous impression. The usual patient with patent ductus is not cyanotic, but on rare occasions when there is a reversed shunt, cyanosis can occur. Electrocardiographic evidence of right ventricular hypertrophy can occur in the latter situation, whereas the usual ductus has a normal electrocardiogram. The occurrence of either a normal axis or left axis deviation in the cyanotic child is a clue to tricuspid atresia. Occasionally the findings of a patient with a high interventricular septal defect may simulate those of an interatrial septal defect and either may simulate an Eisenmenger's complex in early life. Von Gierke's disease is extremely rare, and a more common cause of heart failure in early life in the absence of significant murmurs is endocardial fibrosis. A large heart in a cyanotic patient is more common in transposition of the great vessels than in tetralogy of Fallot. Rales in the lungs and a hacking cough suggest anomalies accompanied by increased pulmonary blood flow. Despite careful examination, an occasional young child with clinical findings consistent with a tetralogy will be found to have complete transposition or pseudotruncus. The importance of adequate fluoroscopic examination is still not appreciated. It is essential to determine whether the pulmonary vascular markings are increased and whether the secondary pulmonary arterial branches pulsate, since this indicates increased flow to the lungs. The opposite findings of decreased vascular markings without pulsations indicate decreased pulmonary blood flow. Often a definite diagnosis cannot be established in the very young until a satisfactory fluoroscopic examination can be carried out with good cooperation of the patient. The left branch of the pulmonary artery will pulsate in an occasional patient with decreased pulmonary flow and cause great confusion.

It is a mistake to assume that all cases of congenital heart disease need to have cardiac catheterization or angiocardiographic studies. The usual case does not. At times, however, these procedures are necessary and must be carried out.

We are now observing cases of congenital heart disease at very young ages when the diagnostic problems are greater. As long as cardiac function is adequate, there should be no great panic as far as the doctor or parents are concerned. As the child grows older the type of defect may become obvious. If not, additional diagnostic procedures can be carried out with greater facility and safety. On the other hand, all steps toward making a diagnosis, including operation, should be carried out in a child who is dying of what is suspected of being a correctible congenital defect.

Pericardial Disease

The pain of idiopathic pericarditis may be misinterpreted as pain due to myocardial infarction or to simple "pleurisy." The characteristic aggravation by respiration and change of position from onset serves to differentiate it from the pain of myocardial infarction. The presence of fever and friction rub at or shortly after onset suggests benign pericarditis rather than myocardial infarction. The occurrence of precordial pain aggravated by breathing several days after onset of myocardial infarction may be due to pericarditis or less commonly to pulmonary embolism and should not be misinterpreted as further myocardial infarction.

Rheumatic pericarditis may or may not be accompanied by pain; the majority have clinical evidence of associated myocarditis. The widespread use of antibiotics has resulted in a decrease in pyogenic pericarditis to such an extent that it may not be considered in differential diagnosis. It is usually secondary to pulmonary infection, and the source may be readily overlooked or masked by antibiotic administration. One should not neglect the occurrence of pericarditis as a manifestation of systemic disease such as collagen disease, leukemia, lymphoma, bronchogenic carcinoma or other neoplastic disease. Tuberculous pericarditis characteristically has an insidious onset, but it is a mistake to think that it cannot begin abruptly with chest pain. Protracted fever, night sweats and weight loss are common. It may at times appear as unexplained

fever or congestive failure. It is common in the absence of parenchymal lung disease and is almost invariably associated with a normal leukocyte count and a positive tuberculin skin test. Although massive pericardial effusion is common, tuberculous pericarditis can occur without detectable effusion, and a pericardial rub may be present even in the presence of considerable effusion. It is usually impossible to differentiate clinically or by x-ray examination pericardial effusion from generalized cardiac dilatation. This is particularly true where there is diffuse muscle disease such as Fiedler's myocarditis, amyloid or collagen disease. The best means of differentiation is by pericardial tap. Tubercle bacilli may be recovered by culture of the pericardial fluid in only about one-half of cases.[12] Unfortunately, cultures may require some weeks and specific therapy should be promptly instituted where clinical evidence favors a tuberculous etiology. Bloody pericardial effusion is commonly due to tuberculosis or neoplastic disease but may occur with any type of pericardial inflammation, including idiopathic pericarditis.[13] In cases of obscure etiology, pericardial biopsy may furnish a clue to the diagnosis.

Heart failure due to constrictive pericarditis may go unrecognized for long periods of time. It should always be considered when the cause of increased venous pressure, hepatomegaly, ascites and edema cannot be readily explained. This is particularly true when there is no orthopnea, and tricuspid valve disease can be eliminated. It is not generally appreciated that dyspnea is the most common symptom and may occur with or without pulmonary congestion. Pulmonary edema is rare except in the small group in which the constriction is localized predominantly to the left ventricle and auriculoventricular groove. The overwhelming majority of cases show a normal or an enlarged cardiac silhouette by x-ray visualization rather than the classic small heart.[14] In a few instances systolic murmurs may be heard at the apex and a mid-diastolic third heart sound is common. The presence of such sounds may cause confusion with rheumatic heart disease. Calcium may be demonstrated in the pericardium in about one-half of the cases with x-ray films taken in the lateral projection. Auricular fibrillation, low amplitude of the complexes and nonspecific T-wave abnormalities may be demonstrated in the electrocardiogram. Right axis deviation is occasionally noted and suggests that the constriction is confined largely to the left side of the heart. A characteristic pressure curve may be obtained by catheterization of the right ventricle[15] and may serve to differentiate constrictive pericarditis from diffuse muscle disease.

Pulmonary Embolism

Pulmonary embolism remains largely unrecognized. It is one of the most important events that can happen in the life of a patient with heart disease. It is most destructive to cardiac reserve and may precipitate heart failure where none existed before, or cause a marked increase in heart failure already present. It should always be suspected when congestive heart failure does not respond to customary therapy. It may produce coronary insufficiency or myocardial infarction in the patient with coronary sclerosis on the one hand and on the other may be misinterpreted as myocardial infarction because of clinical and electrocardiographic similarities. It is not appreciated that pulmonary embolism may cause paroxysmal arrhythmias, particularly auricular fibrillation. The greatest error in recognition results from demanding too much to establish the diagnosis. Thus signs of consolidation in the lung, hemoptysis, positive Homan's sign, persistent calf tenderness occur in perhaps less than half of the cases, and if one awaits the appearance of these the opportunity for early therapy will be missed. In addition to the classic findings, clues to recognition which may be overlooked are: (1) acute pleuritis, (2) syncope, (3) episodes of weakness and sweating, (4) tachycardia out of proportion to fever, (5) paroxysmal auricular fibrillation, (6) refractory heart failure, and (7) repeated attacks of what are thought to be coronary occlusion occurring close together.

Electrocardiogram

In spite of the avalanche of literature on electrocardiography the number of pitfalls has

not decreased. Assuming that one interprets electrocardiograms correctly, errors are made when the limitations of electrocardiography are not appreciated. The greatest error in the use of the electrocardiogram is the failure to realize that 75 per cent of patients with angina pectoris due to coronary atherosclerosis have normal records.[16] The use of the exercise tolerance test brings forth new problems since minor S-T segment changes are common with tachycardia, particularly in the anxious person. It is in this group with atypical chest pain that a search may be so strenuously pursued for objective evidence of disease. The views of Scherf in this regard are pertinent; he disregards changes unless they are marked and unequivocal.[17] It is not commonly appreciated that digitalized patients with normal resting electrocardiograms occasionally develop the S-T force characteristic of digitalis effect after exercise, and simulate the subendocardial injury of a positive exercise test.

The greatest use of the electrocardiogram is the recognition of myocardial infarction. It is particularly useful where definite QRS, S-T and T-wave abnormalities are present. Common errors encountered in this area are as follows: it is not generally appreciated that about 15 per cent of patients with myocardial infarction will demonstrate no electrocardiographic abnormalities. All too often only a single tracing is recorded, and it is not uncommon for electrocardiographic abnormalities to appear several days after an episode of chest pain. At times S-T and T-wave abnormalities are misinterpreted as being due to myocardial infarction, whereas, they may actually be due to pericarditis. A large number of myocardial infarcts produce only T-wave abnormalities. It is here that a large number of mistakes are made. The physician may be so rigid in his electrocardiographic criteria for infarction that he refuses to accept the fact that myocardial infarction can occur with only T-wave changes. At the opposite extreme, others become so alarmed with all T-wave changes that they interpret unimportant findings as grave diagnostic signs. Left bundle-branch block may obscure the QRS findings of myocardial infarction, and this has led to confusion, forcing some to state that infarct cannot be diagnosed if left bundle branch block is present. This is not invariably true since certain S-T and T abnormalities may offer a clue to infarct even in the presence of such conduction disturbance.

It is generally recognized that the current of injury may subside following myocardial infarction. At times, however, marked S-T segment shift may persist for months or years and does not indicate new injury. It is also generally appreciated that ischemic effects of myocardial infarction may subside after several weeks or months. However, it is not common knowledge that definite QRS changes may vanish after months or years, leaving the electrocardiogram completely normal.

Right ventricular hypertrophy as determined electrocardiographically is normal in the newborn and persists for a variable period, perhaps one to two years. Accordingly, abnormal right ventricular hypertrophy cannot be diagnosed until this period has elapsed. Once this period has passed, the electrocardiogram is fairly reliable in indicating right ventricular hypertrophy due to congenital heart disease. It does not aid in determining the etiology of the right ventricular hypertrophy since the right ventricular hypertrophy produced by pulmonary stenosis, pulmonary stenosis with patent foramen ovale, interatrial septal defect, tetralogy of Fallot, transposition of the great vessels and Eisenmenger's complex appears the same. On the other hand, considerable right ventricular hypertrophy may be present due to acquired disease, such as emphysema or mitral stenosis, and the electrocardiogram may remain normal.

Much left ventricular hypertrophy can be present and the electrocardiogram may remain normal. When the mean QRS vector is directed leftward and posteriorly, left ventricular hypertrophy may be suspected when the QRS magnitude is increased. Care must be taken in making such a diagnosis, since the person with a thin chest may have an increased QRS magnitude in the chest leads simply because the recording electrode is nearer the source of electrical energy. When the QRS vector is directed to the left and posteriorly and the mean T vector is oppositely directed, left ventricular hypertrophy may be suspected with or without

increased QRS voltage. This criteria is also fallible since various conditions producing left ventricular ischemia may produce similar findings. The electrocardiogram offers no clue to the cause of left ventricular hypertrophy, since similar findings result from aortic stenosis, aortic regurgitation, essential hypertension and coarctation. The findings of left ventricular hypertrophy in a cyanotic infant or child usually indicates tricuspid atresia.

A patent ductus is usually associated with a normal electrocardiogram. Left ventricular hypertrophy as determined by the electrocardiogram may occasionally occur, but right ventricular hypertrophy is quite rare. Interventricular septal defect is occasionally associated with large biphasic complexes in lead I suggestive of biventricular hypertrophy. Right ventricular hypertrophy may occasionally occur when the interventricular septal defect is high and physiologically simulates an interatrial septal defect.

Right bundle-branch block is usually due to coronary disease but also is produced by interatrial septal defect, pulmonary embolism, and myocarditis. It must never be forgotten that such a conduction defect may be congenital in origin and completely unimportant. Left bundle-branch block is usually due to coronary disease or myocarditis. It may obscure the QRS abnormality of myocardial infarct unless the septum is involved. S-T and T-wave abnormalities due to myocardial infarct may be observed, however, when the infarct is recent.

Pulmonary embolism frequently produces sinus tachycardia without other electrocardiographic abnormalities. At times the nonspecific findings of auricular fibrillation, subendocardial injury, right bundle-branch block, anterior myocardial ischemia are observed. Right ventricular conduction defect may be produced and under certain circumstances has been misinterpreted as posterior myocardial infarction.

During the last year the following misconceptions regarding the electrocardiogram have been encountered:

1. Wrong concepts about congestive heart failure and the electrocardiogram. The electrocardiogram gives no information about the pumping action of the heart.

2. Misconceptions about digitalis and the electrocardiogram. There are no electrocardiographic findings that indicate when a patient needs digitalis. Indeed one should not depend on the electrocardiogram to judge whether a patient needs digitalis, how much digitalis he has had, or if he is fully digitalized. One person may be fully digitalized and the electrocardiogram may remain normal while another subject's electrocardiogram may show the characteristic S-T and T findings due to digitalis after a fraction of the usual digitalizing dose. There is evidence also to indicate that digitalis effect may occur more readily when the heart is abnormal, particularly when there is ventricular hypertrophy. One should never forget that clinical digitalis toxicity can occur without evidence of toxicity in the electrocardiogram, and that electrocardiographic evidence of toxicity can occur without clinical symptoms. Digitalis interferes with the standard exercise test.

3. Misconceptions of establishing etiology from the electrocardiogram. In general, one cannot determine the etiology of heart disease by inspecting the electrocardiogram. For example, clinical data is needed to determine why there is right ventricular hypertrophy.

4. The false concept that treatment can be determined by inspecting an electrocardiogram. There is nothing about electrocardiography that dictates therapy. This is even true when arrhythmias are clearly diagnosed, since the individual who studied only the electrocardiogram would be unaware of previous therapy. There is no treatment, and none is needed, for certain purely electrocardiographic abnormalities such as ventricular ischemia and bundle block.

5. A wrong conception concerning the determination of prognosis from the electrocardiogram. The prognosis of a patient with an electrocardiographic abnormality is that of the underlying disease producing the abnormality. For example, the subject with right bundle block due to a congenital anomaly of the conduction system should live a normal life span whereas the patient with similar right bundle-branch block together with Fiedler's myocarditis has a very poor outlook.

6. The misconception that a normal electrocardiogram indicates a normal heart. As indi-

cated, most errors are in this general area. The prime example of this pitfall is spot-lighted when one recalls that 75 per cent of the electrocardiograms are normal in patients with angina pectoris due to coronary atherosclerosis.

7. A misconception that an abnormal electrocardiogram indicates heart disease. The problem here is failure to appreciate the normal range of any biologic information.

8. The faulty concept that the electrocardiogram always solves a complicated rhythm. Although the electrocardiogram is an indispensable aid to the diagnosis of cardiac arrhythmias, it is not uncommon to see complicated arrhythmias that are very difficult to solve, and at times multiple explanations may be plausible.

Errors in Therapy

Digitalis

Much of the confusion regarding digitalis therapy exists because of the multitude of available preparations. One should master the use of an oral, intramuscular and an intravenous preparation rather than resorting to a variety of preparations. Confusion still exists in determining when a patient is adequately digitalized. This can only be determined by trial and error by giving increased increments of digitalis until a therapeutic response is obtained or minor toxic symptoms develop. In our experience, 0.2 mg. of digitoxin is too much for the average patient, and over a period of time may result in toxicity. When auricular fibrillation is present, the apex rate during mild effort should be used as a guide to adequate digitalization, since the ventricular rate may be normal at rest and unduly accelerated with activity. The presence of ventricular premature beats does not contraindicate digitalis in the patient with heart failure who has not been digitalized; they may disappear following administration of the drug. The presence of myocarditis or myocardial infarction does not preclude digitalis administration; however, it should be used with greater caution. In the presence of myocarditis, thyrotoxicosis, and pulmonary embolism, one cannot determine the dose by the pulse response but must choose an arbitrary dose according to the patient's weight. The young child cannot relate the symptoms of digitalis toxicity and the therapeutic response may not be as clearly defined as in the adult. Accordingly, an average dose based on previous experience must be used.[4]

Digitalis intoxication is commonly overlooked. This is partly due to the lack of appreciation that there may be only a single toxic symptom, and that toxicity may occur without significant electrocardiographic changes. The most common toxic symptom due to digitalis is anorexia, and this may be particularly overlooked when digitalization was instituted at some prior time. The accompanying weight loss over a period of time may be so severe that malignancy may be suspected. Nausea, vomiting, diarrhea, abdominal discomfort and pain, visual disturbances and psychosis may occur and are readily recognized as toxic manifestations. Several days may be required after discontinuing the drug before toxic symptoms subside. Vigorous diuresis of the edematous patient by mercurial diuretics may result in digitalis intoxication. This is due to the loss of potassium as well as to possible mobilization of digitalis. Pulsus bigeminus due to ventricular ectopic beats is the most common arrhythmia due to digitalis. One should not forget that any type of cardiac arrhythmia may result from digitalis therapy. When the pulse rate increases rather than decreases after digitalis, one should be certain that ventricular tachycardia is not present before further drug is given. The loss of potassium by diuresis, vomiting, diarrhea or intubation may precipitate cardiac arrhythmia, particularly in the digitalized patient, even though the serum potassium be within the normal range. Paroxysmal auricular tachycardia with A-V block is particularly prone to occur under such circumstances.[18] The administration of potassium may control the disturbances. A rare patient can tolerate only small amounts of digitalis; it usually helps very little to change types or brands of digitalis.

Nitroglycerin

One of the most common errors in the management of the patient with angina pectoris is the overcautious attitude of the physician regarding the use of nitroglycerin. Patients should be instructed to take the drug promptly and as frequently as necessary. The family must also be instructed in order to avoid undue anxiety.

The initial administration of nitroglycerin should be under observation and the drug given in a dosage of 0.3 mg. to avoid disagreeable side effects that may discourage the patient from using it subsequently. The patient should be urged to use the drug in anticipation of events which frequently bring on pain, for example, just prior to meals or exertion, before bathing, before retiring, prior to intercourse, upon first awakening and prior to situations involving increased emotional stress.

Mercurial Diuretics

Mercurial diuretics are indicated when congestive heart failure is not satisfactorily controlled by digitalis and sodium restriction. These drugs are indicated when there are distressing symptoms that would ordinarily require many hours or days to relieve with digitalis and diet alone. For example, paroxysmal nocturnal dyspnea in a nonedematous patient is an indication for mercurial diuretics. In the patient with congestive heart failure, a record of the weight should be kept, and if an abrupt gain of three pounds occurs, a mercurial diuretic should be administered. Often it may be desirable to administer the drug at regular intervals to prevent the recurrence of congestive phenomena. There may be unjustified reluctance to use mercurial diuretics when albumin and red cells are found in the urine; indeed such therapy may result in clearing of these findings when due to heart failure. Even the presence of chronic renal disease does not preclude their use, although enjoining caution. The nonprotein nitrogen may be elevated to 80 mg. per 100 cc. due to heart failure alone and administration of these drugs may reduce it. It is not common knowledge that chills and fever may rarely follow the injection of a mercurial diuretic. When there is a failure of expected diuresis after an injection, one should suspect electrolyte depletion, particularly when there are symptoms of weakness, drowsiness, muscle cramps, anorexia, nausea and vomiting.

REFERENCES

[1] Viar, W. N., and Harrison, T. R.: Chest pain in association with pulmonary hypertension. Its similarity to the pain of coronary disease. Circulation **5:** 1, 1952.

[2] Kinsey, D., and White, P. D.: Fever in congestive heart failure. Arch. Int. Med. **65:** 163, 1940.

[3] Hyde, Leroy, and Hyde, B.: The diagnostic and therapeutic value of mercuhydrin. Ann. West. Med. & Surg. **3:** 335, 1949.

[4] Logue, B., and Hurst, W.: Congestive heart failure in children. General Practitioner **8:** 41, 1953.

[5] Barrow, G. J.: Treatment of paroxysmal supraventricular tachycardia with Lanatoside C. Ann. Int. Med. **32:** 116, 1950.

[6] Nadas, A. S., and Alimurung, M. M.: Apical diastolic murmurs in congenital heart disease. Am. Heart J. **43:** 691, 1952.

[7] Breese, B. B., Chairman, committee on prevention of rheumatic fever: Prevention of rheumatic fever. Mod. Concepts Cardiovas. Dis. **22:** 1953.

[8] Kumpe, C. W., and Bean, W. B.: Aortic stenosis: a study of the clinical and pathologic aspects of 107 proved cases. Medicine **27:** 139, 1948.

[9] Seabury, J. H.: Subacute bacterial endocarditis experience during the first decade. J.A.M.A. **79:** 1, 1947.

[10] Parsons, W. B., Cooper, T., and Scheifley, C. H.: Occult subacute bacterial endocarditis manifested by hematologic abnormalities, including pancytopenia. Ann. Int. Med. **39:** 318, 1953.

[11] Hunter, T. H.: The treatment of some bacterial infections of the heart and pericardium. Bull. New York Acad. Med. **28:** 213, 1952.

[12] Goyette, E. M., Overholt, E. L., and Rapaport, E.: The treatment of tuberculous pericarditis. Circulation **9:** 17, 1954.

[13] Nathan, D. A., and Dathe, R. A.: Pericarditis with effusion following infections of the upper respiratory tract. Am. Heart J. **31:** 115, 1946.

[14] Chambliss, J. R., Jaruszewski, E. J., Brofman, B. L., Martin, J. F., and Feil, H.: Chronic cardiac compression (chronic constrictive pericarditis). Circulation **4:** 816, 1951.

[15] Yu, P. N. G., Lovejoy, F. W., Joos, H. A., Nye, R. E., Jr., and Majohney, E. B.: Right auricular and ventricular pressure patterns in constrictive pericarditis. Circulation **7:** 102, 1953.

[16] Scarborough, W. R., Mason, R. E., Davis, F. W., Jr., Singewald, M. L., Baker B. M., and Lore, S. A.: A ballistocardiographic and electrocardiographic study of 328 patients with coronary artery disease: comparison with results from a similar study of apparently normal persons. Am. Heart J. **44:** 645, 1952.

[17] Scherf, D., and Schaffer, A. J.: The electrocardiographic exercise test. Am. Heart J. **43:** 927, 1952.

[18] Lown, B. W., Norman, F., Crocker, A. T., Goodale, W. T., and Levine, S. A.: Interrelationship of digitalis and potassium in auricular tachycardias with block. Am. Heart J. **45:** 589, 1953.

ABSTRACTS

Editor: SAMUEL BELLET, M.D.

Abstracters

DAVID I. ABRAMSON, M.D., Chicago
ARTHUR BERNSTEIN, M.D., Newark
RUTH CORTELL, M.D., New York
A. D. DENNISON, M.D., Indianapolis
CHARLES D. ENSELBERG, M.D., New York
ALFRED FROBESE, M.D., Philadelphia
BENJAMIN A. GOULEY, M.D., Philadelphia
RAYMOND HARRIS, M.D., Albany
JOHN C. HARVEY, M.D., Baltimore
J. RODERICK KITCHELL, M.D., Philadelphia
ALDO A. LUISADA, M.D., Chicago
MORTON H. MAXWELL, M.D., LOS ANGELES
VICTOR A. MCKUSICK, M.D., Baltimore
MORTON J. OPPENHEIMER, M.D., Philadelphia
ALFRED PICK, M.D., Chicago
SEYMOUR H. RINZLER, M.D., New York
FRANCIS F. ROSENBAUM, M.D., Milwaukee
ELLIOT L. SAGALL, M.D., Boston
DAVID SCHERF, M.D., New York
JOHN B. SCHWEDEL, M.D., New York
CHARLES R. SHUMAN, M.D., Philadelphia
FRANKLIN SIMON, M.D., Newark
LOUIS A. SOLOFF, M.D., Philadelphia
RALPH M. TANDOWSKY, M.D., Hollywood
S. O. WAIFE, M.D., Philadelphia
MARTIN WENDKOS, M.D., Philadelphia
STANFORD WESSLER, M.D., Boston

BACTERIAL ENDOCARDITIS

Finland, M.: Treatment of Bacterial Endocarditis. New England J. Med. **250**: 372 (Mar. 4), 419 (Mar. 11), 1954.

The author presents a critical review of the current treatment of bacterial endocarditis. Concerning penicillin, it is pointed out that the basic principle of dosage appears to be large doses given continuously over long periods, and although there may be a rough correlation with in vitro sensitivity tests, larger doses than such tests indicate are often necessary. Although oral treatment may be effective for an early infection with a highly susceptible organism, such treatment is too unreliable and requires excessive amounts of the drug. It is felt that repository forms of penicillin do not provide optimum treatment of the disease since the organisms occur in a focal area in dense masses enclosed by fibrin, connective tissue and necrotic material and provided with a poor blood supply. Extremely high levels of penicillin must be provided in the serum to be effective on such a focus of infection. For such infections, effective treatment seems to require intermittent intramuscular injections of large individual doses of the soluble sodium or potassium salts of penicillin at intervals of two to four hours, with the largest doses and shortest intervals being employed for the most resistant organisms or for infections of long-standing. The highest peaks of concentration of penicillin may be achieved by intermittent, fairly rapid intravenous injections, especially if a renal excretory inhibitor such as probenecid (Benemid) is used. The usual effective dose of probenecid is 0.5 Gm. four times daily although twice that amount may be required.

Streptomycin appears to be a useful antibiotic both when used alone against organisms highly sensitive to it and when given together with penicillin for bacterial endocarditis due to organisms moderately sensitive to each of these agents or highly sensitive to one of them. The combination of the two agents may be effective not only by means of the additive or synergistic action but also by delaying or preventing the development of resistance in the organisms to either or both of the agents. Toxic damage to the eighth nerve and hypersensitivity reactions are important considerations when streptomycin or dihydrostreptomycin are used. It appears that bacitracin, in doses of 100,000 units daily in three or four doses together with large doses of penicillin, may prove a useful method of treating patients with endocarditis due to gram-positive organisms which are only slightly or moderately sensitive to penicillin. Nephrotoxicity is the major disadvantage of bacitracin, although in moderate doses this is only rarely disturbing and usually reversible when the drug is discontinued.

The value of the broad-spectrum antibiotics in the treatment of bacterial endocarditis is difficult to determine. Chlortetracycline has appeared to be effective in less than half the cases of infections with *Streptococcus viridans*, in more than half the staphylococcal injections and in only a small proportion of the cases of enterococcal endocarditis. The failures of chlortetracycline have been held attributable to the fact that this drug is bacteriostatic and not bactericidal in the concentrations which can be attained, but other factors, including poor absorption, increased destruction and failure of adequate concentrations to reach the infectious site, may contribute to these disappointing results. Results of

therapy with oxytetracycline in bacterial endocarditis are qualitatively similar to those with chlortetracycline and the mechanism of action and reasons for failure with the two drugs are apparently very similar. Results of treatment of bacterial endocarditis with chloramphenicol have been much the same as those with chlortetracycline and oxytetracycline. It is a common experience with the group of broad-spectrum antibiotics that after apparent clinical improvement and development of negative blood cultures, clinical and bacteriologic relapses may occur either during continued therapy or soon after discontinuance of the antibiotic. The author recommends the use of large doses of penicillin rather than the broad-spectrum antibiotics when initial therapy for doubtful cases of bacterial endocarditis is required or when it is necessary to begin treatment before the results of cultures and sensitivity tests are available. From the reports available so far, it appears that erythromycin and carbomycin are not to be recommended for the treatment of endocarditis even when the infecting organism seems to be quite sensitive to one or the other of these agents in vitro.

The treatment of patients with bacterial endocarditis and negative blood cultures presents several special and difficult problems. Such patients appear to have a higher mortality and a greater incidence of congestive heart failure. From a bacteriologic point of view it is felt that a delay of institution of treatment greater than two to five days is not required if during that period thorough efforts to obtain a positive blood culture are made. Furthermore the treatment of such cases should be vigorous and in a manner similar to that used with an organism demonstrated to be only moderately sensitive to penicillin. Serial observations of the leukocyte counts and erythrocyte sedimentation rates may be the only guides to the adequacy of therapeutic response.

In regard to the prophylactic use of antibacterial agents, the author is of the opinion that the observations available to date do not constitute adequate proof of the value of these procedures in the prevention of bacterial endocarditis. He mentions that at least four cases have been reported in which such treatment failed. It is also possible that while such treatment may reduce the number of susceptible organisms, it may increase the proportion or even the total number of relatively or markedly resistant bacteria. However, it is felt that antibiotic prophylaxis should continue to be used unless it can be shown to be definitely ineffective or harmful. The author also calls attention to the place of surgical treatment in cases of patent ductus arteriosus, mycotic or arteriovenous aneurysms and splenic abscesses. The favorable results from treatment of bacterial endocarditis complicating pregnancy and the puerperium are also mentioned.

ROSENBAUM

Parmley, L. F. Jr., Orbison, J. A., Hughes, C. W., and Mattingly, T. W.: Acquired Arteriovenous Fistulas Complicated by Endarteritis, and Endocarditis Lenta Due to Streptococcus Faecalis. New England J. Med. **250:** 305 (Feb. 25), 1954.

This report is concerned with a 36 year old Negro sergeant who developed multiple arteriovenous fistulas after receiving shell-fragment wounds. This condition became complicated by pseudoaneurysms, endarteritis and ultimately by endocarditis lenta due to *Streptococcus faecalis*. The aortic and mitral valves, which were believed to be normal previously, became extensively involved. The patient died 20 months after the onset of the septicemia despite intensive antibiotic therapy and surgical correction of the vascular defects. The resistance of the enterococcus to antibiotic therapy and its versatility in adapting itself to this therapy by multiple variations is described. The similarity of this case to the experimental production of endocarditis in dogs with arteriovenous fistulas by Lillehei and his associates is mentioned.

ROSENBAUM

BLOOD COAGULATION

Desforges, J. F., and Bigelow, F. S.: An Action of Thrombin on Platelets in Accelerating Clotting. Blood **9:** 153 (Feb.), 1954.

The authors attempted to determine the basis of the effect of thrombin in conjunction with platelets on the acceleration of clotting. They found that washed platelets, after exposure to thrombin preparations or to plasma in which thrombin had been formed, accelerated clotting of hemophilic or of normal blood. This appeared to be due, in part, to increased speed of thrombin formation, resulting from a thromboplastic effect of thrombin-treated platelets. It was believed that thrombin, itself, was not responsible for this special property of treated platelets.

It was concluded that the washed platelets accelerated coagulation in the presence of calcium and that this action was not dependent upon lysis and disintegration of the platelets. Furthermore, it was believed that treated platelets were effective as a substitute for thromboplastin and when so used, increased the conversion of prothrombin to thrombin.

ABRAMSON

O'Brien, J. R.: An Acquired Coagulation Defect in a Woman. J. Clin. Path. **7:** 22 (Feb.), 1954.

Only nine cases have previously been reported of prolonged clotting time in women. The author reports a tenth case, occurring in a 35 year old woman three months after the birth of her first child. The patient developed ecchymoses and painless hematuria. Her clotting time was prolonged and the bleeding time was longer than the average normal

figure for a woman. Laboratory work-up indicated that the defect was due to inadequate conversion of prothrombin to thrombin. There was no evidence for the presence of an inhibitor substance or the absence of the Christmas factor. She appeared to lack antihemophilic globulin, and the platelets were regarded as being abnormal or else there was a possible lack of some plasma substance which normally reacts with platelets to produce thromboplastin. The patient recovered spontaneously in about four months.

ENSELBERG

Herzstein, J., Wang, C., and Adlersberg, D.: Effect of Heparin on Plasma Lipid Partition in Man: Studies in Normal Persons and in Patients With Coronary Atherosclerosis, Nephrosis and Primary Hyperlipemia. Ann. Int. Med. **40**: 290 (Feb.), 1954.

A comparison was made of the effect within two hours of intravenously injected heparin on plasma lipid partition and plasma clearing in 25 individuals. This group consisted of 10 normal men, five patients with atherosclerosis recovering from recent myocardial infarction, seven patients in the nephrotic state of nephritis and three patients with idiopathic hyperlipemia. In five normal subjects with a mean fasting plasma neutral fat content of 315.4 mg. per 100 ml., neutral fat was reduced by 20.7 per cent after 15 minutes and by 33.5 per cent after 60 minutes. In five normal individuals with induced alimentary lipemia and initial mean plasma neutral fat level of 283.2 mg. per 100 ml., there was a drop of 31.7 per cent in this constituent 15 minutes after heparin, an amount larger than one would attribute to physiologic fat clearance in this brief interval. In five patients with coronary atherosclerosis whose mean fasting plasma neutral fat level was 386.2 mg. per 100 ml., heparin injection was followed by a fall in neutral fat of 36.2, 14.3 and 24.7 per cent after 15, 60 and 120 minutes, respectively. A group of patients with nephrosis with a high mean fasting plasma neutral fat content of 838.2 mg. per 100 ml. showed an appreciable reduction in neutral fat after heparin. In three patients with idiopathic hyperlipemia with high plasma total lipids up to 2,090 mg. per 100 ml., varied doses of heparin effected a large and rapid reduction in neutral fat. In this group, the per cent fall in neutral fat within a two hour period after heparin ranged from 23.9 to 60.3 per cent. Light transmission of plasma was associated only in a general way with its lipid content. In patients with nephrosis and essential hyperlipemia, plasma clearing induced by heparin seemed unrelated to the observed fall in neutral fat.

WENDKOS

Bolinger, R. E., Grady, H. J., and Slinker, C. J.: The Effect of Injected Heparin on the Electrophoresis of the Lipoproteins in Patients with Hypercholesterolemia. Am. J. M. Sc. **227**: 193 (Feb.), 1954.

Paper electrophoresis was employed to examine the effect of heparin upon the cholesterol and phospholipid patterns in patients with hypercholesterolemia. Serum was obtained before and after the injection of heparin from four patients with elevated blood cholesterol and one normal subject. In the patient group, the serum cholesterol and phospholipid values decreased. In each instance, the electrophoretic pattern of the lipids following heparin revealed a blunting of the beta-globulin lipid peaks with a shift of the peaks toward the alpha region and an increase in the alpha-globulin lipid peaks. In two of the patients, the cholesterol levels, as obtained by integration from the paper strips, decreased and in the other two patients the values increased. In the case of phospholipid, the values found from the paper strips were increased after heparin. In the hypercholesterolemic cases, the change observed was a decrease in the serum lipids and an increase of these substances in the protein bound phase with changes appearing in the lipoprotein mobilities after heparin. Heparin may influence the protein-lipid binding of cholesterol and phospholipid.

SHUMAN

Ratnoff, O. D., and Potts, A. M.: The Accelerating Effect of Calcium and Other Cations on the Conversion of Fibrinogen to Fibrin. J. Clin. Investigation **33**: 206 (Feb.), 1954.

The effect of calcium ions on the rate of change of fibrinogen to fibrin has been under some dispute. In this study it appears that when ionic strength is maintained at a constant level, calcium and other cations accelerate the conversion of fibrinogen to fibrin by thrombin. Using labeled calcium, it appears that the acceleration of clotting is not accompanied by the formation of a firm bond between the calcium and the fibrin clots.

WAIFE

CONGENITAL ANOMALIES

Vousure, G., Dalhem, J., and Drochmans, P.: Coarctation of the Aorta with Hypertrophy of the Right Cavities. Acta Cardiol. **9**: 157 (Fasc, 2), 1954.

A case is reported of a five year old child with congenital heart disease who died from heart failure and pulmonary complications. Necropsy revealed the coexistence of a complete coarctation of the aorta with a marked hypertrophy and dilatation of the right ventricle and right atrium. Precisely at the site of coarctation, a fibrous band was inserted, corresponding to the obliterated ductus arteriosus. The two anomalies paradoxically involving right and left circulations may represent different coexistent malformations or may be explained on a

common functional basis, if one assumes that the ductus was functioning for a certain period of time after birth.

PICK

Snavely, J. G., and Breakell, E. S.: Fatal Hemorrhage From Esophageal Varices Due to Malformations and Congenital Stenoses in the Portal Venous System. Am. J. Med. 16: 459 (Mar.), 1954.

The authors report the case of a pregnant woman who died following hemorrhage from ruptured esophageal varices. The postmortem examination revealed anomalous development of the portal system which included variations in the positions of the veins as well as multiple strictures, apparently congenital in origin. An explanation of the anomalies on embryologic grounds is postulated.

HARRIS

Oppenheimer, E. H.: The Association of Adult-Type Coarctation of the Aorta With Endocardial Fibroelastosis in Infancy. Bull. Johns Hopkins Hosp. **93:** 309 (Nov.), 1953.

Four infants, dying with adult-type coarctation, also demonstrated endocardial fibroelastosis. Of 14 cases of adult-type coarctation in the literature, three had "endocardial sclerosis" and three had endocardial fibroelastosis. The author proposes that this association indicates that endocardial fibroelastosis is a "congenital malformation" ("developmental defect"). Early demise from coarctation was attributed to the associated endocardial lesion. In three of the four cases, the endocardial changes were limited to the left side of the heart.

MCKUSICK

Tonelli, L., Baisi, F., and Malizia, E.: Pre- and Post-operative Renal Function in Coarctation of the Aorta and Its Relation to the Genesis of Hypertension. Acta med. scandinav. **148:** 35 (Fasc. 1), 1954.

This report is concerned with studies of renal function in five cases of coarctation of the aorta. Three of the cases were studied after operation for this condition, a fourth refused postoperative study and the fifth was not operated upon. In each of the operative cases a preserved aortic homograft was used to restore the continuity of the aorta. Preoperative pressure observations disclosed a systolic-diastolic hypertension in the upper extremities and a very low pulse pressure in the presence of normal or elevated diastolic pressures in the lower extremities; this is considered evidence that the hypertension did not result solely from the mechanical aortic narrowing but that there was a humoral or neurogenic factor which increased peripheral resistance and the diastolic pressure. The cases appeared to fall into two groups so far as renal function studies were concerned. In the first group the renal plasma flow and renal blood flow were in the low normal ranges, there was a slight increase in the efferent resistance, a slight decrease in afferent resistance and a normal filtration factor. In the second group the renal plasma flow and renal blood flow were decreased, the filtration factor and total renal resistance were increased, especially in efferent and venular segments. Surgical treatment normalized the renal functions. The renal changes were considered unlike those in essential hypertension because tubular capacity was preserved and it was the venular and efferent segments whose resistances were increased rather than the afferent ones. Because of their reversibility following removal of the mechanical constriction, the preoperative renal changes were considered functional rather than anatomic and, in fact, secondary to the general haemodynamic changes.

ROSENBAUM

Calo, A.: Congenital Heart Disease and Malformations of the Extremities. Cuore e circolaz. **37:** 303, 1953.

The author presents five cases of congenital malformations of the heart and large vessels associated with various malformations of the extremities. Three were of the acyanotic type (ventricular septal defect) and were associated with polydactyly, microdactyly or camptodactyly. Two were of the cyanotic type. One of them had syndactyly and clinodactyly. The other had several deformities of the hemimelic type, for example, syndactyly, hypodactyly, microdactyly, and clinodactyly.

The type of cardiovascular malformation, the familial character, the electrocardiographic pattern, and the combination of different anomalies, as well as their mechanism, are discussed.

LUISADA

CONGESTIVE HEART FAILURE

Gormsen, J.: Does Rapid Dehydration in Cardiac Decompensation Produce Thromboembolic Complications? Acta med. scandinav. **148:** 61 (Fasc. 1), 1954.

A comparison was made of the incidence of thromboembolic complications in two groups of patients treated for cardiac decompensation in two different hospitals. In the first hospital the treatment was considered intensive and included the use of intravenous Cedilanid and intravenous mercurial diuretics as well as the usual program of bed rest and a salt-poor diet. Of the 116 patients in this first group, 31 per cent died and 14 per cent had a fatal pulmonary complication; 32 per cent of the survivors had thromboembolic complications, nearly one-half of which were pulmonary infarcts. In the second hospital the treatment was more conservative and only one-fourth of the patients received mercurial diuretics intravenously while three-fourths

received digitalis orally, in addition to bed rest and a salt-poor diet. There were 99 patients in this group. There were no thromboembolic complications in the 79 survivors in this group; the mortality was 24 per cent and fatal pulmonary complications occurred in 8 per cent. The author is of the opinion that thromboembolic complications seemed to occur particularly in patients who had intensive treatment and that, in general, those patients with complications showed a larger urine output although this latter correlation was not an absolute one. The author is also of the opinion that the two groups of patients were comparable, although among the patients in the first group there were more elderly persons, more who had been admitted to the hospital previously and more who had received treatment at home prior to admission to the hospital. The author concludes that intensive treatment with Cedilanid and mercurials seems decisive in aggravating the pre-existing tendency to thrombosis and that the actual loss of fluid may be important. It is suggested that in patients in whom dehydration must be intensive, prophylactic treatment with anticoagulants should be considered.

ROSENBAUM

CORONARY ARTERY DISEASE

Schlichter, J., Hellerstein, H. K., and Katz, L. N.: Aneurysm of the Heart: A Correlative Study of One Hundred and Two Proved Cases. Medicine **33**: 43 (Feb.), 1954.

This review was based on a study of 108 ventricular aneurysms occurring in 102 patients. The cases represented 1.8 per cent of the total autopsy population reviewed, and 20 per cent of the total number of cases of myocardial infarction. The incidence of ventricular aneurysm in myocardial infarction reported in the literature varies from 5 to 38 per cent. All the cases in the authors' series were due to arteriosclerotic coronary disease with myocardial infarction.

Aneurysms may be saccular or diffuse, the latter being especially associated with acute formation and with through-and-through infarcts. The size varies from that of a plum to a size larger than the rest of the heart, and may not always exhibit external bulging. The locations of the aneurysms in the authors' series were as follows: apex, 49; anterior wall, 45; posterior wall, 29; interventricular septum, 17. The right ventricle was involved in only four cases. Calcification of the wall was found in two cases, and ossification of the wall and intramural clot in one. Over half the cases showed recent infarction, mostly at the site of the old aneurysm.

The frequency of thromboembolic phenomena was compared with a group of 410 cases of myocardial infarction without aneurysm. These complications were twice as frequent in the aneurysm group (52 per cent). Mural thrombus occurred more than twice as often in the aneurysm group than in the control group. Pericarditis, old or recent, was found in half the cases with aneurysm. This was probably due to subepicardial involvement. No direct relationship was found between pericarditis and thromboembolic phenomena.

Cardiac aneurysm can develop acutely, as shown in two cases in which it appeared two days after acute infarction. The authors found that 73 per cent of cases died within three years, and 88 per cent within five years. They believe that the outlook is twice as unfavorable as for infarction without aneurysm.

Hypertension was found to be twice as frequent in the aneurysm group as in a comparative group of cases of myocardial infarction, and the authors consider this to be of significance. They point out that only 3 of the 22 females with aneurysm were not hypertensive, and of these three patients, two were diabetic.

Over two thirds of the cases of cardiac aneurysms occurred in patients who had a history of no bed rest or less than three weeks of bed rest. This strongly suggests that early ambulation increases the chance for aneurysm. About one in four patients also had significant valvular disease, a greater incidence than is found in myocardial infarction in general; and this too may contribute to the occurrence of aneurysm.

The authors emphasize the fact that though the classic physical signs are often found, none of these signs alone or in combination are pathognomonic, nor does their absence rule out the diagnosis. The roentgenologic signs of aneurysm (enlargement with deformity, bulge, calcification of the wall, angulation, pericardial adhesions, and absent or abnormal pulsations) are very helpful. However, septal and posterior wall aneurysms may escape detection.

The most outstanding finding of the electrocardiographic analysis was that there is no single characteristic pattern of ventricular aneurysm. The most common findings include the residual effects of infarction and persistent displacement of RS-T segments. Other findings include low voltage, periinfarction block, and the pattern of low R_1 with deep S_2 and S_3 associated with T_1 smaller than T_3. Septal aneurysms were frequently associated with conduction disturbances. There was a high degree of correlation between the electrocardiographic location of the infarct and the anatomic position of the aneurysm.

The clinical course of the interim period (from the first infarct to the last illness) was asymptomatic in 44 per cent of cases. In the majority, continuous symptoms of angina pectoris, heart failure or arrhythmias were present. Death was due in over 80 per cent of the cases to recent infarction, heart failure, thromboembolism or to combinations of these. The authors suggest that their data support the use of anticoagulants not only in the terminal

stages of this disease but also in the initial stage, especially when the diagnosis of through-and-through infarct is made. If an effective method could be demonstrated, long-term anticoagulant therapy would be seriously considered. They stress that early ambulation should be avoided, and that bed rest for at least four weeks, if not longer, be mandatory.

ENSELBERG

Siekert, R. B., and Sayre, G. P.: Survival after Occlusion of the Basilar Artery. Proc. Staff Meet., Mayo Clin. **29**: 125 (Feb.), 1954.

Studies were made on a patient who survived thrombosis of the basilar artery. The patient first complained of slurred speech, blurred vision, dizziness and weakness; examination disclosed hemiparesis, hemianesthesia and nystagmus. After partial recovery, he experienced another episode associated with quadriparesis, pupillary inequality, anarthria and aphagia. The patient died eight months later as a result of coronary occlusion. Necropsy disclosed an old organized clot in the basilar artery and extensive infarction of the brain stem.

SIMON

Oliver, M. F., and Boyd, G. S.: The Effects of Estrogens on the Plasma Lipids in Coronary Artery Disease. Am. Heart J. **47**: 348 (Mar.), 1954.

The effects of oral ethinyl estradiol on the lipid levels of 20 hypercholesterolemic men, aged 33 to 67 years, with coronary artery disease were studied in the following manner: (1) a pilot study was made of three men given increasing doses from 0.2 to 0.4 mg. daily over a course of 10 weeks; (2) a long-term study was made of 11 men given 0.1 mg. at 12-hour intervals for two to three weeks and then 0.2 mg. every 12 hours to intolerance as indicated by gynecomastia, listlessness, fatigue and nausea; lipid estimation was done at 7, 17, 27, 27, 51, 65, and 79 days; (3) the short-term study on six men given 1 mg. of drug a day for seven days with lipid estimation 2, 4, 7 and 14 days after the course. The pilot study suggested and the long- and short-term study indicated that a dose 0.2 mg. or more per day of ethinyl estradiol could lower the total plasma cholesterol. No change was noted in functional capacity however.

RINZLER

Losner, S., Volk, B. W., and Wilensky, N. D.: Fibrinogen Concentration in Acute Myocardial Infarction. Arch. Int. Med. **93**: 231 (Feb.), 1954.

The fibrinogen concentration of the plasma in acute myocardial infarction, as studied in 50 cases and determined by the clot density method, correlates well with the clinical picture and allows an estimation of the severity of the disease process at the end of the first week. In gravely ill patients, an increase of the fibrinogen concentration above 800 mg. per 100 cc. has been observed, while relatively mild cases are usually associated with a moderate elevation. The mortality rate is 42.1 per cent in the first group, while in the latter category the corresponding value is 9.7 per cent. This differentiation is not only of value, therefore, in determining the severity of a particular case, but may also offer a more adequate criterion for the institution of anticoagulant therapy.

The erythrocyte sedimentation rate (ESR) on the other hand, frequently fails to show a close correlation with the clinical condition, particularly in very severe cases, in which it may remain normal or rather low. While the fibrinogen concentration returns to normal values in most cases at the end of three weeks, the erythrocyte sedimentation rate continues to display high values in many instances for a long time after the disappearance of active clinical manifestations. In six cases of myocardial infarction complicated by left ventricular failure, the fibrinogen concentration remained increased for prolonged periods of time. In six patients with coronary insufficiency, the fibrinogen concentration remained normal, while the erythrocyte sedimentation rate was either normal or elevated.

BERNSTEIN

Carasso, B., and Longtin, J.: Digestive Studies in Angina Pectoris. Canadian M.A.J. **69**: 364 (Oct.), 1953.

A clinical and statistical study is presented concerning the frequency and the clinical features of digestive symptoms in angina pectoris in the absence of a digestive disease. Whereas nausea, vomiting and secretory troubles are uncommon, flatulence and belching were found to be a fairly frequent complication of angina pectoris. A tentative pathogenesis is offered which ascribes these phenomena either to reflex disturbance or to true aerophagia. Myocardial infarction was found to be proportionately more frequent in patients complaining of flatulence than in the total series. It is believed that in some cases the digestive troubles are a distant sequel of an attack of coronary thrombosis. On this evidence it is felt that a detailed cardiac study is justified in middle aged or aged patients who complain of an aerophagia syndrome of recent appearance.

BERNSTEIN

Kapp, L. A.: Trauma in Relation to Coronary Thrombosis: A Clinical Study of 42 Cases of Coronary Thrombosis Following Trauma or Unusual Effort. Ann. Int. Med. **40**: 327 (Feb.), 1954.

Cardiac injuries include direct or penetrating injuries of the heart, indirect injury of the heart due to a nonpenetrating chest injury, and cardiac injury due to severe, unusual physical exertion or emotional

stress. With this broad concept of cardiac injury there is adequate evidence to support the view that trauma can be a precipitating or aggravating factor in the causation of coronary thrombosis and myocardial infarction. Such a causal relationship could be established in 13 unequivocal cases of acute myocardial infarction encountered by the author and diagnosed by the clinical features and electrocardiographic findings. The contributory role of trauma was predicated upon the occurrence of one of the forms of trauma preceding the acute myocardial infarction, and the onset of cardiac symptoms shortly following the alleged injury. None of the patients died.

WENDKOS

Master, A. M.: The Etiology of Cardiac Enlargement in Coronary Occlusion, Hypertension, and Coronary Artery Disease. Am. Heart J. **47:** 321 (Mar.), 1954.

In an analysis of 500 men who suffered coronary occlusion, 136 had had hypertension, 332 had had normal pressure, and 32 were borderline cases. Seventy-seven of the 500 (15.4 per cent) had definitely enlarged hearts. Of these 77, 29 had hypertension, 45 had normal blood pressure, and 3 were borderline cases. The frequency of cardiac enlargement in those with hypertension was 21.3 per cent; in those with normal blood pressure it was 13.6 per cent. Among the 100 women studied, 44 had enlargement of the heart. The ratio of cardiac enlargement among the women was almost three times that among the men or 44.0 per cent to 15.4 per cent. This higher frequency was found among the hypertensive group (women, 52.2 per cent and men, 21.3 per cent) as well as among those with normal blood pressure (women, 23.8 per cent and men, 13.6 per cent). Hypertension occurred in 71 per cent of the female patients and in 27 per cent of the male patients. Since 71 per cent of the women with coronary occlusion had hypertension, and since 44 per cent had cardiac enlargement, hypertension appears to be an important cause of enlargement of the heart in women. Since 21 per cent of the women had a normal blood pressure, and 23.8 per cent of these had an enlargement of the heart, coronary sclerosis alone appears to be a cause of cardiac enlargement. The combination of hypertension and coronary sclerosis is the most important factor in the causation of enlargement of the heart in patients who suffer from coronary occlusion.

RINZLER

Donald, D. E., and Essex, H. E.: Studies on Chronic Effects of Ligation of the Canine Right Coronary Artery. Am. J. Physiol. **176:** 431 (March), 1954.

Twenty-four per cent of dogs died when the right coronary artery was ligated. Death was from ventricular fibrillation at any time up to 48 hours. The incidence of ectopic beats increased to a peak at 9 to 24 hours. At this time, Q was reduced or absent in I, II, III and aV_f. R was reduced or absent in aV_r. S-T segments were elevated in aV_r and V_1 but were depressed in II, III and aV_f. Infarction of 33 to 77 per cent of the right ventricle caused no detectable decrease in function (catheterization, exercise tolerance). In every case but one, right coronary ligation was followed by extensive collateral development. One month after ligation these interarterial anastomoses were larger than capillaries. Retrograde flow into the ligated vessel occurred immediately. The authors point out that this flow seems essential to the preservation of large areas of myocardium which lie inside the original ischemic and noncontractile area.

OPPENHEIMER

Donzelot, E., Kaufman, H., Danzier, G., and Majerus, N.: Electrophoresis in Myocardial Infarction. Its Biologic Significance and Practical Values. Arch. mal. coeur **47:** 193 (Mar.), 1954.

The electrophoretic pattern of plasma protein fractions and its relation to other humoral disturbances in myocardial infarction is reviewed. The most conspicuous alteration is an alteration of the alpha globulins involving mainly the $alpha_1$ fraction and transiently also the $alpha_2$ fraction. In addition, one may observe the appearance of a particular $alpha_3$ globulin, intermediate between $alpha_2$ and beta, causing some difficulties in the separation of the beta fraction. The increase of alpha globulins appears closely linked to an increase of glycoproteins and seems to have some bearing upon the mobility of blood lipids.

These disorders of the electrophoretic behavior are merely one element among other humoral disturbances in myocardial infarction, which involve, apart from the proteins, the lipid, carbohydrates, electrolytes and the hematopoiesis. All these disorders are of interest to the biologist. From the clinical point of view it is difficult to ascribe to these anomalies any diagnostic or prognostic importance.

PICK

PHARMACOLOGY

Tenney, S. M., and Wedd, A. M.: Disturbances of Rhythm in the Cold-Blooded Heart Under Aconitine. Circulation Research **2:** 28 (Jan.), 1954.

The isolated turtle auricle, exposed to aconitine, exhibited early profound depression of spontaneous rhythmicity, followed in 5 to 20 minutes by a regular tachycardia which persisted beyond one hour. Spontaneous arrhythmias did not develop under aconitine, but single, properly-tuned shocks, during the period of early slowing, elicited a multiple response which appeared electrically like ordinary fibrillation or flutter. Atropine abolished these multiple responses unless the concentration of

aconitine was sufficiently high to have a direct muscle action. Acetylcholine increased the rate and prolonged the duration of the multiple responses initiated by aconitine but, on the other hand, slowed the rate of the late tachycardias which followed aconitine.

Low concentrations of aconitine slow the rate and shorten the refractory period by vagal action, thus creating the circumstances which allow multiple response. In the atropinized auricle, where vagal action is blocked, high concentrations of aconitine (1:500) shorten the refractory period by a direct muscle action. These data support, but do not prove, a re-entrant mechanism in the genesis of auricular fibrillation and flutter. They cannot be explained on the basis of a new focus of high rhythmicity.

MAXWELL

Eckstein, R. W., and Leighninger, S. S.: Chronic Effects of Aorta-Coronary Sinus Anastomosis of Beck in Dogs. Circulation Research **2:** 60 (Jan.), 1954.

Studies were made on 28 dogs at various times up to one year following the operation of Beck (aorta-coronary sinus anastomosis) to determine the chronic effects of the operation.

The graft is capable of retroperfusion of the capillary bed of the left ventricle for about five weeks, after which time, presumably owing to an occlusive process of the veins, it loses its functional contact with the capillary bed. However, significant protection against coronary artery occlusion continues after five weeks because of the development of intercoronary collateral vessels; these intercoronary channels develop during the first few weeks, probably as a result of anoxia, and persist up to one year. The value of a few cubic centimeters of blood per minute, beyond the point of a coronary arterial occlusion, in affording protection of the myocardium is emphasized. It is concluded that in dogs, the Beck operation is protective against the major effects of coronary ligation because of (1) retrograde flow early, and (2) intercoronary anastomoses later.

MAXWELL

Wachstein, M., and Meisel, E.: On the Histochemical Localization of the Mercurial Inhibition of Succinic Dehydrogenase in Rat Kidney. Science **119:** 100 (Jan. 15), 1954.

Renal necrosis can be produced in the rat by the injection of Mercuhydrin sodium in amounts of 10 mg. of mercury per kilogram body weight. The damage appears to be localized within the terminal portions of the proximal convolutions. These authors found a reduction in the histochemically demonstrable succinic dehydrogenase from 45 to 60 minutes after the subcutaneous injection of the drug. The enzyme was absent or reduced in the damaged cells. In contrast, the ascending limbs of Henle's loops retained their full dehydrogenase activity. The results of these experiments support previously expressed views that the microscopically demonstrable effect of mercurial diuretics, even if given in large amounts, is restricted to the proximal convoluted tubules.

WAIFE

Butler, J. J.: Peripheral Vascular Collapse after the Subcutaneous Use of a Hypertonic Nonelectrolyte Solution. New England J. Med. **249:** 988 (Dec. 10), 1953.

The author reports the case of a 48 year old woman who was operated upon for intestinal obstruction. The first postoperative day was uneventful. She received intravenous infusions of 2000 cc. of 10 per cent invert sugar in distilled water and 1000 cc. of Amigen with alcohol. On the second day she was given 1800 cc. of 10 per cent invert sugar solution in distilled water intravenously. The needle was removed inadvertently, and, since veins were difficult to find, the infusion was continued subcutaneously. After she had received 200 cc. of 10 per cent invert sugar in distilled water and 1000 cc. of a solution containing 5 per cent Amigen, 5 per cent glucose and 50 cc. of alcohol in distilled water over a two and one-half-hour period, she was found in peripheral vascular collapse. This responded after several hours to intravenous plasma and blood. The subcutaneous injection sites were swollen, tense, and oozed fluid. There seemed to be more fluid in the area than had been injected. The author explains the sequence of events in this patient as being due to extraction of fluid and electrolytes from the plasma and interstitial fluids in an attempt to preserve isotonicity across membranes. This resulted in the collection of a large quantity of fluid and electrolytes in the thigh regions, where the hypertonic solution was injected and led to acute peripheral vascular collapse. Subcutaneous infusions, therefore, should be limited to isotonic electrolyte solutions to avoid this complication.

SAGALL

Dressler, W., and Kleinfeld, M.: Tic of the Respiratory Muscles. Report of Three Cases and Review of Literature. Am. J. Med. **16:** 61 (Jan.), 1954.

The authors report three new cases of tic of the respiratory muscles and review 17 cases found in the literature. The total of 20 cases included 17 instances of diaphragmatic tic and three cases of tic of the intercostal muscles. The clinical features, mechanism, etiology, diagnosis and treatment of the two types of respiratory tic are discussed. The age of the patients ranged from 9 months to 84 years. The rate of the spastic movements ranged from 60 to 300 per minute. The rhythm of the

spastic contractions was regular only in a minority of cases, notably when the movements of the chest wall or diaphragm were synchronous with, and apparently controlled by, the heart action. The amplitude of the excursions and the force of the spastic contractions were subject to considerable variations even in the same patient. The degree of involvement of muscles varied in different cases. In 12 patients with diaphragmatic tic, fluoroscopy revealed the spastic contractions to be bilateral in eight and unilateral in four. In one patient, both unilateral and bilateral spasms of the diaphragm were observed on successive days. Clinically, pain in the chest, shoulders, extremities and abdomen was a prominent feature in some patients with diaphragmatic tic. In one patient the pain was severe enough to lead to an erroneous diagnosis of coronary thrombosis. Peculiar muscular sounds were heard in instances of intercostal as well as diaphragmatic tic. Tic of the diaphragm may be caused by: (1) disturbance in the central nervous system; (2) stimulation of the phrenic nerve along its course; and (3) a peripheral disturbance which directly stimulates either the terminations of the phrenic nerve or the diaphragmatic muscle. In one case, flutter was confined to a portion of the right leaf of the diaphragm. The authors believed that an altered metabolic state in a portion of the diaphragm might cause an abnormal response to physiologic stimuli.

HARRIS

Harvey, P. A., and Yang, W.: Cardiac Arrhythmia Induced by Epinephrine-Aureomycin in Isolated Frog and Turtle Hearts. Science **118:** 752 (Dec. 18), 1953.

Isolated frog and turtle hearts, perfused with Ringer's solutions containing Aureomycin, or Aureomycin, followed by epinephrine, developed arrhythmias. Time was a factor in these studies because if epinephrine was given 20 minutes after Aureomycin, the effects on the heart were noticed 10 minutes later when the pressor effect had almost disappeared. When the time interval was increased to 40 minutes, the irregularities became more pronounced. When the time interval was 80 minutes, complete heart block occurred. Potassium chloride administration just before epinephrine perfusion abolished the arrhythmias. Although the explanation for this finding is not on hand, there is some work that suggests that the energy-liberating mechanism that causes myocardial contraction may have been disrupted by the antibiotic.

WAIFE

Wald, M. H., Fierro, M. I., and Keeton, K. H.: Toxic Effects of 1-Hydrazinophthlazine in Ambulatory Hypertensive Patients. Am. Heart J. **46:** 861 (Dec.), 1953.

Eleven ambulant patients with hypertension (nine women and two men) were given Apresoline in doses ranging from 150 to 500 mg. daily in divided quantities. Dosage was begun at 12.5 mg. three times daily. Most patients had a systolic blood pressure over 200 mm. Hg and a diastolic pressure over 100 mm. Hg. Eight of the 11 patients experienced toxic symptoms including severe headache, faintness, dyspnea, anorexia, nausea, weakness, angina pectoris, paresthesia and epiphora. No significant alterations of the patients' urinalysis, hemogram, electrocardiogram, ocular fundi, or gross cardiac dimensions were observed. No chronic toxicity was noted.

RINZLER

Wakim, K. G., Denton, C., and Essex, H. E.: Certain Cardiovascular Effects of Vasopressin (Pitressin). Am. Heart J. **47:** 77 (Jan.), 1954.

Pitressin was administered intravenously in doses of 0.1 to 1 unit per kilogram of body weight either at once, or during a period of 30 minutes, to dogs which were anesthetized with pentobarbital sodium. Cardiac output was determined by application of the Fick principle. Systolic and diastolic blood pressures at various points in the heart or pulmonary vessels were recorded by means of strain gages connected to cardiac catheters. Another strain gage recorded the blood pressure from a needle inserted into the femoral artery. The blood flow was recorded in heparinized animals from one or both femoral arteries by use of bubble flowmeters.

Administration of Pitressin produced definite reduction in cardiac rate, consumption of oxygen, venous content of oxygen and cardiac output. Sometimes the heart became arrhythmic, and extrasystoles appeared soon after injection of Pitressin. Initially, transient increases were noted in both systolic and diastolic blood pressures in the femoral artery. This was soon followed by increases in the systolic and diastolic pressures in the pulmonary artery, in the wedge pressure in the small pulmonary vessels and in pressures in the left atrium, while pressures in the femoral artery decreased to less than control values and the pulse pressure was much reduced. Administration of Pitressin produced great reduction in femoral blood flow.

RINZLER

Silverthorne, M. C., and Moyer, J. H.: Observations on the Diuretic Effect to Parephyllin (R-3588), Neohydrin, and Mercuhydrin When Administered Alone and in Combination. Am. J. M. Sc. **227:** 83 (Jan.), 1954.

The use of Parephyllin, a theophylline derivative, was not found to have any augmenting effect upon the action of mercurial diuretics in patients who are responsive to this therapy. Parephyllin was found to have a transient and mild diuretic action when

employed alone. By the oral route, both aminophylline and Parephyllin did not produce a significant increase in the 24-hour water and sodium excretion in congestive heart failure patients. Neohydrin, an orally effective mercurial agent, was compared to parenterally administered Mercuhydrin. The oral preparation was about 50 per cent as effective in removing water and 75 per cent as effective in removing sodium as was Mercuhydrin.

SHUMAN

Fowler, P. B. S., Guz, A.: Blood Pressure and the Effect of Hexamethonium. Brit. Heart J. **16:** 1 (Jan.), 1954.

The authors show that each patient of 30 normal and 40 hypertensive subjects has a constant pattern of response of the blood pressure to exercise, and this pattern remains unchanged under the influence of hexamethonium bromide. Hexamethonium, however, is capable of reducing the peak blood pressure on exercise. The authors, therefore, believe the postural effect induced by the methonium compounds is of major importance in the control of the blood pressure by these drugs.

SOLOFF

Greisheimer, E. M., Oppenheimer, M. J., Ellis, D. W., Lynch, P. R., and Shapiro, L.: The Effect of Ether on Cyclopropane-Epinephrine Arrhythmias. Anesthesiology **15:** 51 (Jan.), 1954.

Ventricular arrhythmias were induced in dogs under cyclopropane-oxygen anesthesia by intravenously administered epinephrine solutions. Once the required dose of epinephrine was determined, the heart was allowed to resume its basic rhythm. Ether was then added without changing the rate of flow of cyclopropane. After about 30 minutes, epinephrine was again injected and continuous recordings were obtained. Other measurements recorded consisted of pulmonary arterial and aortic blood pressures, blood concentrations of cyclopropane and ether, blood oxygen and carbon dioxide content. In 15 cases, the first injection of epinephrine resulted in ventricular fibrillation. This was not related to the concentration of cyclopropane in the blood, the dose of epinephrine, or the duration of anesthesia. A bigeminal rhythm was the most common irregularity observed after the injection of epinephrine. The ectopic ventricular beat was able to open the pulmonic valve but not the aortic semilunar valve. In most cases, the first ectopic beat originated in the upper anterior right ventricle. These epinephrine-induced arrhythmias were not related to either hypoxia or the accumulation of carbon dioxide in the blood. In 18 experiments, ether prevented the occurrence of epinephrine-induced arrhythmias in 13, and delayed the onset or shortened the duration in the remaining five.

SAGALL

Deterling, R. A., Ngai, S. H., Laragh, J. H., and Papper, E. M.: The Cardiovascular Effects of Continuous Intravenous Infusion of Norepinephrine, Epinephrine and Neosysnephrine during Cyclopropane and Ether Anesthesia in the Dog. Anesthesiology **15:** 11 (Jan.), 1954.

The authors studied the cardiovascular effects of continuous intravenous infusions of vasopressor amines in seven dogs under ether anesthesia, and at a later date under cyclopropane anesthesia. Anesthesia was induced by thiopental sodium. Pressor effects were observed with norepinephrine, epinephrine, and Neo-Synephrine with cyclopropane anesthesia, but not consistently or as marked with ether anesthesia. The pressor effect of norepinephrine was more marked than that of epinephrine. The simultaneous administration of cyclopropane and norepinephrine resulted in all studies in ventricular arrhythmias, especially premature ventricular contractions, and also ventricular tachycardia. With epinephrine, ventricular arrhythmias were found in only 5 out of 12 tests, and not recorded in three simultaneous infusions of Neo-Synephrine and cyclopropane. With ether anesthesia, the infusion of these vasopressor amines did not alter the basic sinus rhythm.

SAGALL

Rothschuh, K. E.: Occurrence and Functions of Acetylcholine in the Heart. Klin. Wchnschr. **32:** 1 (Jan.), 1954.

The author reviewed the present state of knowledge and the theories concerning the role of acetylcholine in cardiac physiology. Bound as preacetylcholine to proteins (or lipids) it is a normal component of cardiac fibers. This compound is subject to persistent metabolic alterations which are accelerated during cardiac activity. These alterations are caused by a system of enzymes, a catabolic esterase and an anabolic acetylase. Variations in the equilibrium of this system play a pertinent part in the functional capacity and in the contraction of cardiac muscle.

The action of acetylcholine in the process of excitation of, and conduction by, cardiac fibers can be visualized as follows: Acetylcholine, liberated at the cell membrane from its bound form by action potentials of an approaching impulse, changes the permeability of the membrane. This results in abolition of the resting membrane potential and local changes of the polarity of the cell surface. Acetylcholine is then inactivated by acetylcholinesterase. With restitution of the membrane potential acetylcholine is resynthetized by the anabolic ferment and incorporated in its inactive form into the cell membrane. The metabolic changes in the acetylcholine system are subject to variations under the effect of vagal stimulation. Subsequent to electrical "bombardment" from terminal afferent vagal fibers, acetylcholine is liberated in relatively

large amounts. This quantitive alteration causes a disturbance in the normal balance and time sequence of enzyme action, which in turn causes alterations in the threshold of excitability and in the duration of refractoriness of fibers involved. With a very high local concentration of acetylcholine, propagation of the impulse will be blocked. Since warmblooded animals do not have vagal innervation of the ventricles the content of acetylcholine will be higher in the atria. This, however, is not true for the cold-blooded animal.

The role of acetylcholine in the process of contraction is not well understood. It could be that acetylcholine liberated in the course of electrical activation enhances the function of adenosine triphosphate, which in turn speeds up the reaction of the contractile substance actomyosin.

PICK

Zeeman, S., Hirsch, S., and Bellet, S.: The Effect of Potassium Depletion Induced by Desoxycorticosterone Acetate on the Lethal Dose of Lanatoside C in Dogs: Relationship of Plasma Levels, Skeletal and Cardiac Potassium Content to the Lethal Dose. Am. J. M. Sc. **227:** 65 (Jan.), 1954.

An extensive study was conducted to examine the influence of lowered body potassium content upon digitalis sensitivity, to evaluate the effect of digitalis upon myocardial potassium content, and to determine whether tolerance to digitalis is related to intracellular, or extracellular potassium levels. It was found that potassium-depleted dogs (DOCA-treated) showed an increased sensitivity to lanatoside C when compared with the control animals. The mean lethal dose of lanatoside C in potassium-depleted animals was not correlated with serum potassium levels but was correlated with the skeletal muscle content of this ion. It was of interest to note that muscle potassium increased after lanatoside C administration in the potassium-depleted animals but did not increase in the control group. Contrary to other reports, the authors noted no decrease in the myocardial potassium content after toxic doses of the glycoside.

SHUMAN

Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H.: Rheumatic and Febrile Syndrome during Prolonged Hydralazine Treatment. J. A. M. A. **154:** 23 (Jan. 2), 1954.

A reaction occurred in 13 of 139 patients under prolonged and intensive treatment with hydralazine hydrochloride (Apresoline). Its milder phase resembled early rheumatoid arthritis, and its more severe form simulated aspects of acute systemic lupus erythematosis. The milder form of the process usually disappeared spontaneously on withdrawal of therapy, or on reduction in dosage. The severe form was controlled with cortisone and corticotropin. The mechanism of the syndrome is obscure. The probability is, however, that the entire picture is a toxic response to the use of hydralazine.

KITCHELL

Steven, R. J. M., and Tovell, R. M.: Hexamethonium Salts as an Aid to the Orthopedic Surgeon. J. A. M. A. **154:** 402 (Jan. 30), 1954.

The use of hexamethonium salts in orthopedic surgery to reduce blood pressure and so reduce blood loss is discussed. The authors have found that a small test dose of 3 to 5 mg. of hexamethonium compounds is frequently sufficient to produce postural hypotension, and further small doses of a like order are administered as required. A satisfactory hypotension can be maintained by this method with the systolic blood pressure at approximately 80 mm. Hg. These compounds had no deleterious effect on the heart in 91 patients undergoing major orthopedic procedures included in this series.

KITCHELL

PHYSICAL SIGNS

Dressler, W., Kleinfeld, M., and Ripstein, C. B.: Physical Sign of Tight Mitral Stenosis. J. A. M. A. **154:** 49 (Jan. 2), 1954.

A heaving systolic pulsation of the precordial area over the right ventricle is described as a physical sign associated with tight mitral stenosis. This is caused by the forceful action of a markedly enlarged right ventricle which is pushed towards the anterior chest by the dilated left atrium. The pulsation can be recognized merely by inspection and palpation and, when accompanied by auscultatory findings of mitral stenosis, is indicative of "tight mitral stenosis."

KITCHELL

Little, R. C., Hilton, J. G., and Schaeffer, R. D.: The First Heart Sound in Normal and Ectopic Ventricular Contractions. Mechanism of Closure of the A-V Valves. Circulation Research **2:** 48 (Jan.), 1954.

Phasic right atrial and right ventricular pressures and heart sounds were simultaneously recorded from the exposed dog heart. Both normal beats and ventricular beats without preceding atrial contractions were studied. Heart sounds and electrocardiograms were recorded from humans.

The first heart sound is significantly delayed in the absence of atrial systole. The time between onset of the ventricular pressure rise due to ventricular contraction and the beginning of the first heart sound is minimal at normal A_S-V_S intervals. These data support the view that, following atrial systole, there is a reversal of the atrial-ventricular pressure gradient before the onset of ventricular contraction. As a result, the A-V valves are closed or nearly closed before ventricular systole. In

ectopic ventricular beats, the A-V valves are closed from an open position by ventricular contractions.

MAXWELL

PHYSIOLOGY

Semple, R. E.: Effect of Small Infusions of Various Dextran Solutions on Normal Animals. Am. J. Physiol. **176:** 113 (Jan.), 1954.

Dextran, lost from vessels and appearing in the urine, is related inversely to the mean molecular weight of the injected substance. After six hours, all dextrans leave the circulation at the same rate. This later part of the disappearance curve may be metabolic. All dextrans have a similar effect on plasma volume, red cell volume, plasma protein, nonprotein nitrogen, sodium, potassium and red cell hemoglobin. Increase in plasma volume due to dextran is less than the volume injected; the increase lasts for more than one hour but less than six. Total potassium and nonprotein nitrogen are increased just after infusion but are at control values one hour later. Other changes are not significant.

OPPENHEIMER

RHEUMATIC FEVER

Soulié, P., Bouvrain, Y., Fortin, P., Di Matteo, J., and Tricot, R.: Rheumatic Activity Provoked by Commissurotomy. Arch. mal. coeur **47:** 49 (Jan.), 1954.

Among 100 instances of mitral commissurotomy, there were 10 cases with definite or probable reactivation of rheumatic fever. Four patients who either had no history of rheumatic fever or one dating back many years developed fever, arthralgia, pericarditis and laboratory signs of activity shortly after surgery. In two other similar cases symptoms and signs developed several months after commissurotomy. In two instances, the operation was performed in a stage that was not completely quiescent, and, hence, the postoperative course, suggesting rheumatic activity, could not be definitely related to the surgical procedure. The rest developed postoperative complications which were not definitely rheumatic in nature.

A review of the operative notes revealed no relationship of these complications to the type of lesion found at surgery or the operative difficulties encountered. All patients recovered, though some only after several months. In all, the results of surgery eventually turned out to be either excellent or satisfactory. Thus, from the prognostic standpoint, this type of reactivation appears to be benign and has no adverse effect on the outcome of the operation.

PICK

Besterman, E. M. M. The Cardiac Output in Acute Rheumatic Carditis. Brit. Heart J. **16:** 8 (Jan.), 1954.

The cardiac output during and after exercise did not change in 10 individuals with active rheumatic carditis, but it did increase in seven after recovery. The author concludes that active rheumatic carditis impairs the functional efficiency of the myocardium.

SOLOFF

Wallis, A. D., and Viergiver, E.: Serum Phospholipid and Rheumatic Fever. Am. J. M. Sc. **227:** 171 (Feb.), 1954.

The average serum phospholipid levels in childhood were found to be lower than in adults. The effectiveness of the serum inhibitor of streptolysin S depends in part on phospholipid, which is lowest at the usual time of onset of rheumatic fever. The importance of this relationship lies in the suspicion that streptolysin S may represent a cause of this disease. In studying 178 patients with inactive rheumatic heart disease, serum phospholipid was found to be lower than the normal average for the age. Dietary histories showed that the ingestion of eggs was low in a high percentage of patients with rheumatic disease. This was considered significant because of the importance of eggs as a source of choline used in phospholipid formation. It is suggested that rheumatic fever is produced when a hemolytic streptococcal infection produces more streptolysin S than the natural phospholipid-derived serum inhibitor is able to neutralize.

SHUMAN

Wallis, A. D.: Dietary Eggs and Rheumatic Fever. Am. J. M. Sc. **277:** 167 (Feb.), 1954.

The author believes that serum phospholipid is a component of the natural inhibitor of the streptococcal hemolysin known as streptolysin S. Because eggs are the richest dietary source of dietary choline which may be important in the synthesis of phospholipid, dietary surveys with regard to eggs were taken in 184 patients with rheumatic heart disease and 1380 normal persons. By the recall method, the author feels that 40 per cent of the cardiac patients ate few eggs in childhood as compared with 16 per cent of the control subjects. A history of the restriction of eggs in childhood was given by 49 per cent of those requiring digitalis for the control of heart disease and by 51 per cent of those who had had three or more acute episodes of rheumatic fever. Individual differences in choline intake and requirements may be of significance in determining the susceptibility to rheumatic fever.

SHUMAN

Drury, M. I., O'Driscoll, M. K., Hanratty, T. D., and Barry, A. P.: Rheumatic Heart Disease Complicating Pregnancy. Brit. M. J. **1:** 70 (Jan. 9), 1954.

One hundred and seventy-five patients with rheumatic heart disease complicating pregnancy (a

total of 250 pregnancies in a four-year period) were observed in Dublin where contraception, therapeutic abortion, and sterilization are not practiced. In addition, the patients were drawn from the underprivileged groups with poor home conditions, no home help and a high degree of fertility. These cases represented 1.7 per cent of all cases of pregnancy. In 220 registered ("booked") cases there were no deaths. This emphasizes the importance of diagnosis and prenatal care.

Of six deaths during pregnancy or within a year after, five were primigravidae. Three had aortic regurgitation. (Aortic regurgitation was present alone in one patient and with mitral stenosis in 23 others. One hundred and fifty-one had mitral stenosis.) One patient died of subacute bacterial endocarditis 10 weeks after delivery. The proneness of the primigravidae to reactivation of rheumatic fever (because of their younger age) is probably a significant factor in this result.

The authors conclude that sterilization and therapeutic abortion should play no role in the management of this situation.

McKusick

ROENTGENOLOGY

Davison, P. H., and Epps, R. G.: The Left Auricular Electrokymogram in Mitral Stenosis. Brit. Heart J. **16:** 49 (Jan.), 1954.

In a study of 29 individuals with mitral disease and 10 normals, the left auricular electrokymogram was found valueless in differentiating between pure mitral stenosis and mitral stenosis with regurgitation.

Soloff

Dimond, E. G., and Gonlubol, F.: Medical Intelligence: Death Following Angiocardiography. Report of Two Cases after Administration of Diodrast and, Neo-Iopax, Respectively. New England J. Med. **249:** 1029 (Dec. 17), 1953.

The authors report two fatalities occurring after the administration of dye for angiocardiography. A 43 year old woman with right ventricular hypertrophy, patent foramen ovale, mitral stenosis, drainage of the right pulmonary veins into the right atrium, and right bundle-branch block became cyanotic and complained of a warm sensation immediately after 60 cc. of a 70 per cent concentrated Diodrast solution had been rapidly administered intravenously. No heart sounds could be heard and the patient died, despite coramine and artificial respiration. Skin sensitivity tests had been negative. Preparatory medication had consisted of quinidine, cortisone, and Seconal. A 9 year old boy with cor pulmonale due to pulmonary endarteritis received 27 cc. of a 75 per cent Neo-Iopax intravenously. His pulse suddenly became imperceptible after 45 seconds. Intracardiac epinephrine restored normal rhythm, but cardiac arrest appeared again within 30 seconds. Pronestyl, cardiac massage, and electric defibrillation were not successful in re-establishing normal cardiac rhythm. Arrhythmias varying from auriculoventricular dissociation to ventricular tachycardia and ventricular fibrillation were recorded until death three hours later. Preparatory medication had consisted of quinidine and Nembutal, and skin sensitivity tests had been negative. The authors believe that since they encountered two fatalities in approximately 100 angiocardiograms, and had no serious complications in 300 cardiac catheterizations, the latter is the diagnostic procedure of choice if possible. The danger of death with angiocardiography should limit this procedure only to those patients in whom there is an imperative need (in terms of therapeutic value) for the diagnostic information that only angiocardiography can supply.

Sagall

SURGERY

Helden, R. A., Kirklin, J. W., and Gifford, R. W.: The Treatment of Abdominal Aortic Aneurysms by Excision and Grafting. Proc. Staff Meet., Mayo Clinic **28:** 707 (Dec.), 1953.

The majority of aneurysms arising from the abdominal aorta are arteriosclerotic; the syphilitic type is less common. Arteriosclerotic abdominal aortic aneurysms are seen most frequently in males in the later decades of life. The poor prognosis accompanying this disease cannot be too strongly emphasized. The aim of the numerous forms of surgical treatment used in the past has been to control enlargement and rupture of these aneurysms by reinforcement of the wall of the aneurysmal sac, from either within or without. These various methods generally have been unsatisfactory.

Two cases are presented, and three others are mentioned, in which arteriosclerotic abdominal aortic aneurysms, arising below the origin of the renal arteries, were removed and replaced by a preserved homologous aortic graft. Although this form of surgical treatment is practical, and seems to be ideal theoretically, a longer follow-up of the condition of patients treated by this method will be necessary to prove its true worth.

Simon

Carter, M. G., Gould, J. M., and Mann, B. F., Jr.: Surgical Treatment of Mitral Insufficiency—An Experimental Study. J. Thoracic Surg. **26:** 574 (Dec.), 1953.

Experiments were conducted on 26 mongrel dogs which were subjected to 38 operations. The experiments were divided into two groups. In the first group, an effort was made to place a plastic ball encased in a pericardial tube between the mural leaflet and the endocardial surface of the lateral ventricular wall. There were 10 of these experiments. In the first seven, the prothesis oc-

cupied a poor position in relation to the mural leaflet or failed to penetrate the myocardium completely. With further experience it was possible to introduce the pericardially encased ball through the ventricular wall so that it consistently came to rest in the recess behind the center of the mural leaflet.

In the second group of eight experiments, a longer pericardial tube was fashioned allowing the ball to penetrate further into the ventricular chamber. This permitted the prosthesis to swing to and fro synchronously with the directional changes in blood flow, approximating a ball valve mechanism. This maneuver was performed in four animals as an acute experiment. It was performed in four other animals as a survival experiment under aseptic conditions, and these animals were sacrificed at intervals ranging from five days to two months.

The authors then attempted to produce mitral regurgitation and to correct this defect immediately by insertion of the pedicled ball valve. In some experiments regurgitation was produced by incision of either the mural or septal leaflet. In other cases, the margin of the mural leaflet and its chordae tendineae were sutured to the ventricular wall. The degree of regurgitation was assessed both by the operator's finger within the left auricle and by pressure tracings obtained through a polyethylene catheter connected to a recording electromanometer.

No change was observed in the left auricular manometric pressure pattern of normal animals in which the plastic prostheses were used. Significant pressure and wave pattern changes were observed in animals with previously created mitral insufficiency following the insertion of pedicled balls. The accuracy of intracardiac finger palpation in determining the volume of regurgitant flow is questioned. Finally, the viability of an intraventricular pericardial pedicle is doubtful even when the pericardial flap is carefully cut to preserve its normal blood supply.

DENNISON

Miller, B. J., Gibbon, J. H., Greco, V. F., Smith, B., Cohn, C. H., and Allbritten, F. F., Jr.: The Production and Repair of Interatrial Septal Defects under Direct Vision with the Assistance of an Extracorporeal Pump-Oxygenator Circuit. J. Thoracic Surg. **26:** 598 (Dec.), 1953.

This report demonstrates that interatrial septal defects in animals can be successfully created and repaired under direct vision with an open cardiotomy while the cardiorespiratory functions are maintained by a mechanical heart and lung apparatus during the period of caval occlusion. In addition, the danger of air embolism can be avoided by what appears to be a safe and practical method through the employment of a plastic tube vent.

The cardiorespiratory functions of 29 dogs have been maintained by an extracorporeal blood circuit while the right atrium was widely opened and an interatrial septal defect created under direct vision. The septal defect was not repaired in five dogs. Three of these survived and were sacrificed at 23, 44 and 51 days. There was no spontaneous closure or significant decrease in size of the defects. In the other 24 dogs, the septal defect was closed by a pericardial graft immediately after creation of the defect. Fourteen dogs survived and were sacrificed at varying intervals up to 157 days. In all instances, the defect was completely closed, the graft well healed and covered with endothelium on both sides.

In 12 consecutive experiments a plastic tube vent was placed in the left ventricular chamber during the period in which the left atrium was exposed to atmospheric air. Air embolism of the coronary arteries did not occur in any of these experiments. In the 17 experiments in which the left atrium was exposed to atmospheric air in the absence of a left ventricular vent, air embolism of the coronary arteries occurred in five dogs. Three of the five dogs died. Ventricular fibrillation occurred in the five dogs with coronary air embolism. It did not occur in any other animal.

DENNISON

Swann, W. K., Lomasney, T. L., and Rodriguez-Arroyo, J.: The Management of the Dangerously Torn Auricle. J. Thoracic Surg. **27:** 96 (Jan.), 1954.

The utilization of the left auricular appendage as an avenue of approach to the diseased mitral valve has been widely adopted in the treatment of mitral stenosis. The operative procedure has been fairly well standardized, the technic is relatively simple, and the procedure is generally a safe one. However, there are certain normal and pathologic variations in the auricle and its appendage which may render the procedure extremely hazardous. Any one or a combination of these factors may result in a tear in the auricle, and this tear may readily extend below the previously applied purse string.

In a series of 40 mitral valve commissurotomies, two instances of hemorrhage from a dangerously torn auricle were encountered. It is emphasized that the surgeon in his haste to arrest hemorrhage from a torn auricle may possibly create an irreversible situation by application of a clamp across the coronary vessels. Blood loss can be controlled by occlusion or compression of the torn auricle with the operative hand, while preparations are then made for rapid intra-aortic blood replacement before definitive closure of the defect is attempted. These tears can then be managed safely under direct vision.

DENNISON

Kaunitz, V. H., and Andersen, M. N.: An Experimental Study of the Effect of Parasympathetic Denervation of the Lung on Pulmonary Artery Pressure. J. Thoracic Surg. **27:** 55 (Jan.), 1954.

Because of the dearth of knowledge of the mechanisms regulating the lesser circulation, it was thought useful to study changes in the pulmonary vascular bed following complete parasympathetic denervation of the lung in the experimental animal. This study was facilitated by the availability of a measurement of complete parasympathetic denervation of the lung. This test consisted of determining the presence or absence of the Hering-Breuer reflex unilaterally during bronchospirometry.

Ten healthy mongrel dogs were studied by means of the described ventilatory test, and by cardiac catheterization preoperatively, and after parasympathetic denervation of both lungs. Complete parasympathetic denervation of both lungs was accomplished by dividing only the vagus branches to each lung. Completeness of the denervation was proved by demonstrating the bilateral absence of the Hering-Breuer reflex postoperatively. A decrease in pulmonary artery pressure was observed as the result of this pulmonary parasympathetic denervation. This would indicate that the parasympathetic innervation of the lung has a significant role in the regulation of blood pressure in the lesser circulation. Whether this is a direct or indirect effect is not known.

DENNISON

Johnson, J., and Kirby, C. K.: Prevention and Treatment of Cardiac Arrest. J. A. M. A. **154:** 291 (Jan. 23), 1954.

When the circulation of the blood to the brain stops, the surgeon has approximately four minutes in which to act. It is important for every anesthetist and every surgeon to familiarize himself with the essential points concerning cardiac arrest so that he will be able to act promptly. For all practical purposes, the causes of cardiac arrest may be placed in the following categories: reflex phenomena, an overdose of or sensitivity to an anesthetic agent, hypoxia, or a combination of these factors. It appears that the most important prophylactic measure is the avoidance by the anesthetist of hypoxia and hypercapnia in the patient. The surgeon should avoid strong traction on thoracic and abdominal viscera and the risk of sudden hemorrhage should be minimized. Operations on the heart are feared because of the danger of ventricular fibrillation. However, it appears that the securing of maximum oxygenation of the myocardium before direct trauma to it is the most important protective measure against ventricular fibrillation. The surgeon should be prepared to expose the heart through the left side of the chest if the blood pressure and pulse suddenly and unexpectedly disappear. If there is not too great a delay in instituting adequate artificial circulation and respiration, normal rhythm should be resumed in a short time. If ventricular fibrillation is present, it is most effectively dealt with by electric shock after the myocardium has been adequately oxygenated.

KITCHELL

Berne, R. M.: Myocardial Function in Severe Hypothermia. Circulation Research **2:** 90 (Jan.), 1954.

The functional status of the myocardium in hypothermia was investigated by means of pulse contours recorded from the left ventricle, the left atrium and the aorta of anesthetized, open-chested dogs partially immersed in ice water.

Good pressure contours were maintained even with extreme degrees of cooling and did not exhibit any of the characteristics of circulatory failure, thus demonstrating that the arterial pressure decline in hypothermia is not a manifestation of myocardial failure. The striking changes induced were the marked prolongation of systole and of isometric relaxation. At low temperatures, increases in heart rate from 10 to 60 beats per minute produced by atrial stimulation seriously interfered with cardiac filling. This was largely due to reduced ventricular filling-time and the elimination of the atrial contribution to cardiac filling. It is suggested that acceleration of the heart in severe hypothermia is contra-indicated. The data support the contention that hypothermia, as employed in cardiac surgery, does not seriously interfere with myocardial competence, provided its natural slow rhythm is maintained.

MAXWELL

Soulié, P., Joly, F., Carlotti, J., and Sicot, J. R.: The "Pulmonary Capillary Curve" and Clinical Data in 17 Observations of Verified Mitral Regurgitation. Arch. mal. coeur **47:** 1 (Jan.), 1954.

A study of pulmonary wedge pressure curves in 250 cases of mitral disease revealed 15 instances in which the contour of the curve and the timing of its components suggested the presence of mitral regurgitation. Seven cases were submitted to surgery and regurgitation was confirmed in six. On the other hand, slight or moderate regurgitation was found by the surgeon in 17 patients among 120 cases who had commissurotomy. Thus the registration of a systolic mitral reflux in pulmonary capillary pressure curves is an inconstant but a highly diagnostic finding, and its presence indicates a marked degree of mitral insufficiency.

Correlation of wedge pressure curves with physical, radiologic and electrocardiographic findings with regard to the diagnosis of mitral insufficiency revealed that no single sign, per se, is diagnostic, but the association of several findings permits the diagnosis with a high degree of accuracy. Recogni-

tion of some mitral insufficiency in the presence of a tight stenosis of the valve has no great practical importance and does not influence the outcome of surgery. If, however, the stenosis is only moderate, mitral regurgitation may be aggravated by the operation. As a rule, such an aggravation is revealed only in cardiodynamic postoperative studies and remains clinically latent.

PICK

Poppe, J. K.: Reinforcement of Aortic Aneurysms by Wrapping. J. Thoracic Surg. **27:** 36 (Jan.), 1954.

Repeated animal experiments during the past five years have indicated that the greatest perivascular fibrosis is obtained by using polyethylene film which is heavily impregnated with dicetyl phosphate on both sides.

Laboratory and clinical experience with wrapping, patching and wiring aneurysms has indicated that the application of polyethylene film containing dicetyl phosphate represents the most satisfactory method of treating aortic aneurysms. Admittedly, the film can rarely be placed completely around the aneurysm. It does not reduce the size of the aneurysm, it does not prevent the extension of the aneurysm with rupture in another area, and it does not prevent rupture under the patch for a period of from four to six weeks postoperatively. Wrapping is best suited to fusiform aneurysms of the descending aorta below the arch where large branches are less numerous. Even with these limitations, wrapping affords a greater chance for relief of symptoms, prevention of rupture, and avoidance of fatal operative complications to a greater number of patients than any other method except resection.

DENNISON

Thompson, S. A., and Plachta, A.: Fourteen Years' Experience with Cardiopexy in the Treatment of Coronary Artery Disease. J. Thoracic Surg. **27:** 64 (Jan.), 1954.

The authors have recently made a 14 year follow-up study of 57 patients who had had a cardiopexy. In order to determine fully the effects of the operation, no patient has been included in this series who has been operated upon during the past 12 months. Seven patients died during the operation or while convalescing, giving an operative and hospital mortality of slightly more than 12 per cent. Thirty-three of the patients, or 66 per cent, are living at the present time.

Of the 50 patients who have been followed up to the present time or to the time of their death, 37 were men and 13 were women. This is a ratio of slightly less than 3 to 1. The youngest patient was a woman 35 years old, the oldest was a woman 68 years of age. The average age of the entire group was 51 years, the majority of the patients being in the sixth decade.

Almost all of these patients were terminal cardiac cases and more or less completely incapacitated. Few of them were satisfactory as surgical risks. As the result of operation, 90 per cent of the patients were improved more than 50 per cent, and 40 per cent were more than 75 per cent improved. There are indications that in addition to their physical improvement, the patients who died during this study lived longer than would have been expected without surgery.

DENNISON

Dodrill, F. D.: Experience with the Mechanical Heart. J. A. M. A. **154:** 299 (Jan. 23), 1954.

The mechanical heart can perform four different types of substitutions for the heart and lung. These consist of: (a) bypass of the right side of the heart, (b) bypass of the left side of the heart, (c) bypass of both sides of the heart while the lungs continue to perform their functions, and (d) bypass of the heart and lungs while the mechanical oxygenator performs lung functions. A discussion of these various ways of using the mechanical heart is presented. Four patients have been successfully operated on by one of these procedures. The pulmonary valve on the right side and the mitral valve on the left side have been successfully exposed and surgically corrected with survival of the patients.

KITCHELL

Cliffton, E. E., Grossi, C. E., and Cannamela, D.: Lysis of Thrombi Produced by Sodium Morrhuate in the Femoral Vein of Dogs by Human Plasmin (Fibrinolysin). Ann. Surg. **139:** 52 (Jan.), 1954.

The authors investigated the effect of plasmin solution (a combination of streptokinase, streptodornase and plasminogen) on experimentally produced thrombi using sodium morrhuate. In nine dogs, segments of femoral vein were isolated and then filled with the sclerosing solution. At varying times after a thrombus had formed, plasmin solution was injected into the systemic circulation. None of the animals showed any serious reaction to the material other than mild to moderate oozing of blood from the fresh wounds. In six dogs no sodium morrhuate was injected, and in these the intravenous administration of plasmin solution also caused oozing from raw surfaces.

In the case of the animals in whom thrombi had been produced, the latter were completely lysed by the injection of 2.8 to 5.1 mg. per kilogram of body weight. A marked increase in spontaneous lytic activity was observed in the whole blood of all dogs studied.

ABRAMSON

Fremont, R. E., Luger, N. M., Surks, S. N., and Kleinman, A.: Treatment of Surgical Shock with Arterenol. Arch. of Surg. **68:** 44, (Jan.), 1954.

L-Arterenol was given in continuous intravenous infusion to 22 patients in shock of different causes. It was found to be of distinct value in cases of shock due to acute surgical abdominal conditions, those with operative and postoperative shock, and in those with advanced hemorrhagic shock. It brought such patients out of shock when added to fluid replacement therapy which in itself had been ineffective.

The authors found that 8 cc. of a 1:1000 solution of *l*-Arterenol (that is, 8 mg. of *l*-Arterenol in 1000 cc. of isotonic sodium chloride or in 5 per cent dextrose in distilled water) is safe and practicable. The pulse and the blood pressure have proved to be of value in following patients being treated with *l*-Arterenol. Following infusion the pulse returns to more normal values. This may not be observed, however, in atropinized patients. In addition, the patient can now maintain his own blood pressure when the infusion is stopped for about 10 or 15 minutes. If the systolic pressure remains above 90, it may be possible to stop the infusion.

Infusion with the drug may be kept up for many hours or even days. The only adverse reaction noted has been sloughing of skin, resulting from extensive soft tissue infiltration of the solution. However, the basic cause of the shock must be treated with the usual fundamental measures. *L*-Arterenol must not be expected to take care of continuing hemorrhage, etc.

DENNISON

Helmsworth, J. A., Clark, L. C., Jr., Kaplan, S., and Sherman, R. T.: An Oxygenator-Pump for Use in Total By-Pass of Heart and Lungs. J. Thoracic Surg. **26:** 617 (Dec.), 1953.

In the experiments described in this report, it was not primarily planned to obtain long survival of the animal subjected to extracorporeal oxygenation and circulation. The first objective in this series was the continuation of laboratory evaluation of the Clark oxygenator-pump. The second objective was to acquire further experience in opening the cardiac chambers while the animal's functions of respiration and circulation are being carried out by artificial means. In the final part of this presentation, a report is given of the clinical application of this machine. A complex defect in the cardiac septa was corrected by direct operative procedure through a right auricular cardiotomy.

The machine flow rates and animal temperatures in 17 experiments were tabulated. Results given of analysis showed that oxygenation was obtained at the rate of 3.67 cc. per minute per kilogram, and that carbon dioxide was eliminated at the rate of 2.99 cc. per minute per kilogram. Experience in dealing with the coronary venous return and the hazard of air embolism in the open and bypassed heart were presented. The problem of excessive volume of coronary venous return of the right side of the heart was dealt with initially by catheter drainage of the coronary sinus. In several animals, however, the coronary return to vessels other than the coronary sinus comprised so large a volume that the auricle was inadequately emptied by simple coronary sinus drainage. The next method that was tried for emptying the right auricle was continuous suction in the dependent portion of the chamber. At that stage in the evolution of the procedure, the hazard of air embolism became more apparent and a further modification in method was tried. This was to maintain continuous suction in the right ventricle by means of one of several glass and plastic catheters which served to withdraw the coronary venous blood. It also prevented the propulsion of air emboli into the pulmonary artery, since the pressure in the right ventricle was reduced by continuous suction and the instrument separated the leaves of the tricuspid valve. The "blind" cannulation of the chamber through the tricuspid was somewhat hazardous because of the possibility of trauma to the endocardium. In addition to this risk, it was soon noted that no matter what aspirating device was employed for that purpose, it added to the complexity of a restricted operative field. An alternate procedure which lacked these disadvantages was temporary occlusion of the pulmonary artery. This vessel was occluded by means of a ligature just beyond the pulmonic valve. The complications of air embolism were not prevented by continuous aspiration of the bronchial and coronary venous blood from the dependent portion of the left auricle. After failure of this measure, the next method tried was that of total occlusion of the aorta. Obstruction of the aorta at the lowest level of its extracardiac portion prevented propulsion of air emboli into the major circulation. Closure of the aorta, however, interrupted the filling of the coronary arteries from the arterial stream of the extracorporeal circuit. Failure of this second method led to the trial of a third precaution against the development of air embolism. The aorta was catheterized with an additional plastic tube of small diameter. The tip of this instrument was localized just above the aortic valve, thus serving as a special channel for the return of arterialized blood from the apparatus to the proximity of the coronary orifices. An adequate flow of arterial blood into the coronary circuit was thus assured, and the aorta was then occluded in its ascending portion by ligation and compression of its walls around the central catheter. This, however, did not prevent the ventricle from ejecting blood with air admixed into the occluded root of the

aorta. Thus, the problem of air embolism remains unsolved.

DENNISON

THROMBOEMBOLIC PHENOMENA

Seligman, B.: Pulmonary Embolism Complicating Trypsin Therapy. New England J. Med. **250:** 23 (Jan. 7), 1954.

The author reports the case of a 40 year old male who was admitted to the hospital with an acute left iliofemoral thrombophlebitis of seven days' duration. He was treated with an anticoagulant, prophylactic sulfonamide, and local treatment for a tinea-pedis infection. The prothrombin was maintained at 34 per cent for ten days. Procaine penicillin was administered for six days but was stopped because of a generalized urticaria. After seven days the patient had shown considerable improvement and was allowed out of bed. On the tenth day, however, signs of active phlebitis again became apparent. Ten mg. of trypsin was dissolved in 250 cc. of distilled water with 5 per cent glucose and given intravenously. A similar infusion was administered again that day and on the two following days. No infusions were given on the fourth day, but two were given on the fifth. Four hours after the last infusion a pulmonary infarction developed on the right side. Thus, in this case, pulmonary embolism developed during treatment with trypsin.

SAGALL

Svien, H. J., and Karavitis, A. L.: Spontaneous Thrombosis of the Right Internal Carotid Artery Diagnosed by Arteriography. Proc. Staff Meet., Mayo Clinic **29:** 13 (Jan.), 1954.

Spontaneous thrombosis of the internal carotid artery is not frequent. It is difficult to estimate its incidence since many patients who have this condition are suspected of having an expanding intracranial mass, an aneurysm or some type of cerebrovascular accident. The cause of spontaneuos thrombosis of the internal carotid artery often is unknown. In some patients arteriosclerosis of thromboangiitis obliterans has been incriminated. It is pointed out that inflammatory lesions or tumors in the region, aneurysmal formation in the aorta or parent trunks, syphilis, embolism and trauma are not present as etiologic agents in spontaneous thrombosis of the internal carotid artery. In the 69 cases reported, the underlying lesion was arteriosclerosis.

Most authors report a greater incidence in males, a predilection for the left side and an occurrence that is most frequent in the middle-age group. Explanation for the left-sided predilection is lacking; however, the difference in anatomic relationships of the two vessels in the neck has been suggested as a factor.

SIMON

Owen, W. R., Thomas, W. A., Castleman, B., and Bland, F.: Unrecognized Emboli to the Lungs with Subsequent Cor Pulmonale. New England J. Med. **249:** 919 (Dec. 3), 1953.

The authors present 12 cases in whom chronic cor pulmonale and congestive heart failure developed as a result of obstruction to the blood flow in the lungs because of multiple and mainly "silent" pulmonary emboli.

In these cases extensive old pulmonary embolism had led to hypertrophy of the right ventricle in the absence of other complicating diseases which might have led to cardiorespiratory impairment. Five cases illustrating the typical features of this syndrome are reported in detail.

The clinical picture in this group of patients was usually that of increasingly severe congestive heart failure of undetermined etiology. Dyspnea and cough were frequent symptoms and usually appeared before there was evidence of right ventricular hypertrophy. Hoarseness and syncope were encountered in only one case respectively. Five of the 12 patients had at least one episode of hemoptysis, but actual infarction of the lung was not an important finding in this group of patients. Right ventricular heart failure, as manifested by pulsating neck veins, enlargement of the liver and extensive ankle edema, appeared late in the course of the illness. Ascites was noted in 6 cases. Cyanosis appeared in 10 out of the 12. Clubbing and polycythemia were encountered infrequently and were only of a slight degree. Common auscultatory findings consisted of accentuation of the pulmonic second sound, gallop rhythm, and harsh systolic murmurs along the left sternal border in the third or fourth intercostal space. X-ray studies showed relative ischemia of the lung fields in five cases and, in most cases, prominence of the main pulmonary vessels and enlargement of the right ventricle. In 11 cases electrocardiograms were available and 10 showed the findings of right ventricular hypertrophy. Right bundle-branch block was not found. All the patients expired because of intractable congestive heart failure.

Postmortem examination showed marked hypertropy of the right ventricle. Relatively insignificant pulmonary infarcts of varying age were found in five cases. Extensive and extreme degree of pulmonary embolization of varying sizes, ages, and locations were the most constant findings. In 10 cases, one or more large branches of the pulmonary artery contained emboli, and, microscopically, all 12 showed organized emboli in the tertiary branches of both lungs. In nine cases a source of the pulmonary emboli was demonstrated—the leg veins in six, the heart in two, and anastomatic veins between an obstructed portal vein and vena cava in one patient.

The authors point out that similar cases have been reported in the past as primary pulmonary

arteriosclerosis, primary pulmonary hypertension, or Ayerza's syndrome. This study suggests that a large proportion of these cases may result from latent pulmonary embolization occurring over many years, rather than from the very rare "primary" disease of the pulmonary arteries.

SAGALL

Barnard, P. J.: Thrombo-embolic Primary Pulmonary Arteriosclerosis. Brit. Heart J. **16:** 93 (Jan.), 1954.

Thromboplastin extracted from rabbit brain tissue was injected into the 20 young adult rabbits and 140 white mice. Twenty-eight of the mice were given one lethal dose and 112 mice received 2 to 12 injections at three- to four-day intervals. The rabbits were similarly injected. Sections of the lungs taken from these animals showed lesions of thromboembolic arteriosclerosis corresponding closely with those described and illustrated in human cases of primary pulmonary arteriosclerosis. Other lesions, probably anaphylactic, were also encountered. The author believes that some human cases of severe pulmonary arteriosclerosis with right ventricular hypertrophy and failure might be due to protracted embolism by minute fibrin clots.

SOLOFF

VASCULAR DISEASE

Pycke, D. A.: Dissecting Aneurysm of the Aorta. Recovery after Treatment with Hexamethonium. Lancet **6797:** 1189 (Dec. 5), 1953.

A case of clinically diagnosed dissecting aortic aneurysm with hypertension was described in which hexamethonium bromide was administered and the patient recovered. Since death in a first attack is nearly always due to external rupture, it may be worth trying hexamethonium treatment in cases where the patient is hypertensive and survives long enough to reach the hospital.

MAXWELL

England, D. L.: Rupture of Aortic Aneurysm into Superior Vena Cava. Arch. Int. Med. **92:** 897 (Dec.), 1953.

A review of the literature disclosed 117 previous cases of rupture of an aortic aneurysm into the superior vena cava. The usual clinical appearance and findings as obtained from these reports are presented, and an additional case is reported. Symptoms begin with the sudden onset of a moderate to severe superior vena cava obstruction syndrome. Physical examination presents the striking appearance of moderately severe edema, venous distention, and cyanosis sharply limited to the head, neck, arms, and upper chest, in a dyspneic, seriously ill patient. Although the aortic valve is almost always intact and competent, peripheral signs of aortic insufficiency are often present, due to rapid dissipation of the arterial blood pressure into the superior vena cava. A murmur, usually the characteristic continuous machinery type of an arteriovenous shunt, is heard over the aneurysm and a thrill may be associated with systole. Contrary to what might be anticipated pulsation of the congested neck veins is reported to have occurred in only about 10 per cent of the cases. Laboratory findings commonly disclose a positive serologic test for arm-to-tongue circulation time. Oxygen saturation studies by cardiac catheterization or comparison of peripheral blood values provide clinching evidence. Roentgenographic studies reveal the pulsating shadow of the saccular aneurysm. The clinical course after the rupture has occurred is usually steadily downhill, ending in death. However, a few patients have lived for several months, and three are reported to have survived apparently on the basis of collateral circulation development. No specific therapy alters the course of the disease. One attempt at surgery was unsuccessful, but perhaps future development in surgical technics may make this approach feasible in some cases.

BERNSTEIN

Barker, W. F.: Mycotic Aneurysm. Ann. Surg. **139:** 84 (Jan.), 1954.

The author reported a study on five cases of mycotic aneurysms. In order for this condition to occur, two factors are necessary: (1) mural damage of the vessel, either on the basis of embolism, obstruction of the vasa vasorum, atherosclerosis, congenital defects or external trauma; and (2) sepsis, which may come from infected emboli or a bacteremia, or may be due to a contiguous infection. Once the aneurysm has developed, generally it rapidly enlarges and then ruptures, although on occasion spontaneous thrombosis may occur.

Clinically, local pain and a pulsating mass may be present, with a systolic bruit heard over the lesion. Arteriography may be useful in establishing the diagnosis. Treatment consists of excision of the involved segment of vessel. Prognosis is poor partly because of the seriousness of the underlying disease and partly because of the inaccessibility of most of the aneurysms. The recent use of antibiotic therapy makes more of these lesions amenable to surgical procedures. However, it can be expected that a large number of patients will succumb before the appropriate operation can be performed.

ABRAMSON

Johnston, J. B., Kirklin, J. W., and Brandenburg, R.O.: The Treatment of Saccular Aneurysms of the Thoracic Aorta. Proc. Staff Meet., Mayo Clinic **28:** 723 (Dec.), 1953.

By far the majority of thoracic aortic aneurysms are still of syphilitic origin, but it can be expected that trauma, particularly in view of the increasing number of automobile accidents, will supply an even larger proportion. Arteriosclerotic aneurysm

of the thoracic aorta is rare. The average period from the onset of symptoms to death in a series of 188 thoracic aortic aneurysms was six to nine months. Even this brief reprieve is one of relentless progression, during which the patient may become increasingly breathless and have increasingly severe pain. It is the very occasional aneurysm which becomes filled with solid clot spontaneously, and even clotting is no permanent guarantee of safety.

In view of such a grave forecast, some radical approach is called for in the treatment of these aneurysms. Historically, the methods of surgical approach are numerous, but presently three methods are worth while. These are: (1) production of a clot within the aneurysm; (2) external reinforcement; and (3) removal of the aneurysm, followed by suture of the defect, or replacement by a graft. Intrasaccular clotting is achieved by inserting a long piece of wire into the sac, depending on the presence of the wire alone to produce thrombosis, or augmenting the effect by passing an electric current through the wire. External reinforcement is an attempt to provide a bastion for the aneurysmal wall by promoting fibrosis through the use of plastic sponge, cellophane or its active principle dicetylphosphate. No attempt is made to expose the aneurysm fully, but the accessible portions are overlaid with sheets of the material. Removal of the aneurysm is the most logical and ideal approach. It is the authors opinion that resection should be performed for all saccular aneurysms.

SIMON

Janes, J. M.: The Treatment of Peripheral Aneurysms. Proc. Staff Meet., Mayo Clinic **28:** 718 (Dec.), 1953.

For practical purposes peripheral aneurysms are of two main types: (1) traumatic or false and (2) arteriosclerotic. One rarely finds an aneurysm which may be classified as mycotic or one which is due to syphilis. Laceration of an artery which is not repaired may give rise to traumatic aneurysm. This type is also called a false aneurysm as the sac does not consist of the walls of the artery but of the condensed and thickened tissues around the artery. Most of the peripheral aneurysms which are seen at the Clinic, however, are based on arteriosclerosis; for example, 92 of the 100 popliteal aneurysms studied were arteriosclerotic.

Generally, when a peripheral aneurysm has been diagnosed, it should be treated surgically. It has been said that spontaneous cure of an aneurysm by thrombosis may occur. To depend on such a cure, however, involves great risk as is illustrated in a case of a thrombosed popliteal aneurysm which was encountered—the patient's leg had to be amputated.

SIMON

Glenn, W. W. L., Hampton, L. J., and Goodyer, A. V. N.: Use of Controlled Hypotension in Large Blood Vessel Surgery. Arch. of Surg. **68:** 1, (Jan.), 1954.

Three general methods of producing hypotension have been used: arteriotomy, total sympathetic blockade by high spinal anesthesia, and ganglionic blockade. Of the three methods, the latter is the most physiologically sound and one of the most widely used. Until recently, hexamethonium compounds have been generally employed but have the disadvantage of too prolonged vasodilatation. Therefore, a shorter-acting drug was sought, and the authors report the use of Arfonad in seven patients undergoing surgery for closure of a patent ductus and in one patient who had resection of an aneurysm of the ascending aorta.

This method was used only in older children or in adults when the ductus was unusually large and short or the aorta adjacent to the ductus was dilated and thin-walled. Hypotension was produced in all but one patient who had constant intravenous infusion of Arfonad in 0.1 per cent solution and 5% dextrose in water. The amount of solution administered was dependent on the response to the drug of the blood pressure of the individual patient. The blood pressure was permitted to return to a normotensive level prior to closure of the chest. A short-acting vasopressor substance is obviously preferable, particularly when sudden hemorrhage may occur and when suture lines must be tested at normotensive levels.

The influence of a hypotensive agent on a dilated and thin-walled aorta is dramatic. During controlled hypotension the aorta decreases visibly in size.

It was of interest to determine whether the pressure in the pulmonary artery might not be affected by the administration of the hypotensive drug. There was a prompt fall in pulmonary artery pressure after the ductus was occluded and an even greater fall with the ductus occluded after the administration of Arfonad.

DENNISON

OTHER SUBJECTS

Mortensen, J. D., Grindlay, J. H., and Kirklin, J. W.: The Arterial Homograft Bank. Proc. Staff Meet., Mayo Clinic **28:** 713 (Dec.), 1953.

In lieu of a practical autograft of some type or an effective prosthetic device, in recent years satisfactory early results have been obtained by the use of arterial homografts. In this technic segments of aorta or large arteries are removed aseptically from acceptable donors within a few hours after death, preserved in one manner or another and then implanted as arterial grafts to replace removed segments of a comparable vessel.

Most clinical experience has been accumulated with homografts stored by the refrigeration method. Its chief disadvantage is that it is wasteful, since

grafts can be preserved only for relatively short terms—probably about six weeks. After this time has elapsed, the graft may be softened, friable and have an increased tendency toward thrombosis; hence, it must be discarded. The deep-freeze method is rather cumbersome and in some hands has produced grafts with an increased tendency toward thrombosis. However, it has the very real advantage that grafts may be stored for prolonged periods, months probably, before use. If adequate technical care is taken, assuring rapid freezing and rapid thawing, sufficiently low temperatures, and avoidance of partial dehydration or crystallization, this method evidently will give grafts entirely as satisfactory as those preserved by the refrigeration method.

In addition to the keeping of accurate descriptive records for each graft, the following controls are carried out before the graft is implanted; histologic sections are studied for evidence of abnormalities of the donor artery, and it is insisted that results of bacteriologic cultures of the original saline wash, of the storage media 24 hours after the graft is stored and again 48 hours before it is to be used, are negative. At the time of implantation the graft must be elastic, tough and have a smooth, normal-appearing intima.

SIMON

Master, A. M., Jaffe, H. L., and Chesky, K.: Relationship of Obesity to Coronary Disease and Hypertension. J. A. M. A. **153:** 1499 (Dec. 26), 1953.

Persons with heart disease or hypertension who are obese have a much higher mortality rate than those who are of average weight or below. The relationship of obesity to heart disease is reviewed using new standards of weight and of hypertension for the general population. In patients in private practice, there was a definite increase in the relative frequency of overweight in men with coronary disease, including angina pectoris, coronary insufficiency, and coronary occlusion. Obesity produces a strain on the heart and is capable of aggravating coronary disease. It is significant that there was a low incidence of overweight among patients who had made a long-lasting, complete functional recovery from coronary occlusion and insufficiency. Overweight occurred more frequently in hypertensive men than among the general population. In women with hypertension and/or coronary disease, obesity was not more frequent than in the normal population. This observation is being investigated in a large series of women. At present the reason for the possible difference between the sexes is not obvious. The development of coronary disease in hypertensive women may not be influenced by obesity. The authors feel that although obesity occurs more commonly in patients with hypertension or coronary disease no definite conclusion concerning the etiologic relationship can be drawn. However, the importance of avoiding obesity in cardiovascular disease is clearly indicated.

KITCHELL

Reynolds, S. R. M.: Homeostatic Regulation of Resting Heart Rate in Fetal Lambs. Am. J. Physiol. **176:** 162 (Jan.), 1954.

This study deals with fetal lambs in the last third of gestation. There was no correlation of heart rate with age. Bilateral vagotomy decreased the heart rate and lowered the blood pressure. Stimulation of the cut ends produced bradycardia. Occlusion of the umbilical arteries to produce circulatory distress established vagal tone. The response outlasted the occlusion and was not blocked by eliminating carotid sinuses or by cardiac sympathectomy. In the denervated fetal heart, asphyxial bradycardia was followed by longlasting tachycardia. In one fetus, bilateral adrenalectomy abolished the tachycardia. The author suggests that the in utero fetus is protected from stress which contributes to the development of vagal tone in adults.

OPPENHEIMER

Singer, H., Sporn, J., and Necheles, H.: Fatty Acid Absorption and Chylomicrons. Science **118:** 723 (Dec. 11), 1953.

The authors studied oleic acid absorption in intact dogs and dogs with Thiry's fistula. When oleic acid was added to the Thiry loop, chylomicronemia began one hour after administration and continued for four hours. The chylomicronemia after oral administration was of somewhat greater magnitude than in the previous experiment. The addition of bile salt gave rise to a greater degree of chylomicronemia, especially when compared with the absorption of oleic acid from the fistula in the absence of bile.

The authors conclude that oleic acid is absorbed through the lymphatics. Bile salts may not be necessary for long-chain fatty acid absorption but may enhance it.

WAIFE

Sigler, L. H.: Cardiac Disability and Death Caused by Strain: Problem in Workmen's Compensation. J. A. M. A. **154:** 294 (Jan. 23), 1954.

There is much controversy on the causal relationship between physical and emotional strain and cardiac disability and death. Such causal relationship should be considered established when a severe strain is followed by acute cardiac symptoms and definitely demonstrable acute myocardial damage. An honest history of the events leading to an attack is most essential in establishing causal relationship. The incidence of clinical recovery from an acute myocardial insult and the rate of continued employment is high. If another acute coronary insult

with myocardial injury occurs in the course of usual activity after complete clinical recovery from an insult due to strain, the second attack cannot be attributed to the original strain, but should be considered a spontaneous insult in the course of progressive coronary degeneration. If the second attack occurs after unusual strain, the cardiac injury should be attributed to the second rather than the first attack. Varying degrees of disability may often follow a cardiac injury due to strain. The extent of disability should be gauged primarily by the degree of underlying coronary disease, the extent of residual permanent myocardial damage, and the functional capacity of the heart.

KITCHELL

Zoob, M.: The Esophageal Pulse in Mitral Valve Disease. Brit. Heart J. **16:** 39 (Jan.), 1954.

The author attempted to establish the diagnosis of mitral regurgitation by simultaneous registration of the esophageal pulse and electrocardiograms in 27 normals, 13 patients with left ventricular hypertrophy of hypertensive or aortic origin, 15 with auricular fibrillation, 9 with innocent systolic murmurs, 14 with pure regurgitation, 24 with mitral stenosis and 17 with mitral stenosis and regurgitation.

a, c, and v waves are present in the esophageal pulse analogous to those of the jugular phlebogram.

In the normal, the apex of the V wave does not precede the second heart sound, whereas, in 10 of 14 patients with mitral regurgitation it did precede the second heart sound. The diagnosis of regurgitation in the presence of mitral stenosis cannot be made by the esophageal pulse which was abnormal in 20 of 41 with mitral stenosis.

A systolic plateau is attributed to auricular stasis, congestive heart failure or auricular fibrillation.

SOLOFF

Lindgren, P., and Uvnäs, B.: Postulated Vasodilator Center in the Medulla Oblongata. Am. J. Physiol. **176:** 68 (Jan.), 1954.

The distal part of the medulla was stimulated electrically in anesthetized cats and dogs to elicit depressor responses. The depressor area in these experiments was larger than previously discovered, and stimulation was accompanied by skin and muscle vasodilation. Evidence is presented to support the statement that vasodilation depends on inhibition of vasoconstrictors. When both so-called vasodilator centers are cauterized, the depressor responses to buffer nerve stimulation are blocked. This is not true of sensory spinal nerves. The opinion is expressed, as a result of these experiments, that this area does not govern vasodilator activity nor does it relay inhibitory impulses to the vasoconstrictor center. This area probably contains vagal and sinus fibers inhibitory for the vasoconstrictor center. A pressor area is situated ventral to this depressor area. This may consist of vagal and sinus fibers excitatory for the vasoconstrictor center, or of such neurons connecting with depressor fibers.

OPPENHEIMER

Friedman, R. L.: Infrapulmonary Pleural Effusions. Am. J. Roentgenol. **71:** 613 (Apr.), 1954.

The author reports 17 cases of infrapulmonary pleural effusions simulating an elevated diaphragm or large collections of pleural fluid. The diagnosis may be established by abdominal injection of air outlining the location of the diaphragm; by insufflating the stomach with carbonated beverages or introducing air through a Levin tube for left-sided effusion; or by shifting of the fluid away from the bases to the chest wall in lateral recumbent positions.

The author offers an explanation for these localized effusions. He believes that all pleural effusions are initially infrapulmonary, and that with increased amounts of pleural fluid there is overflow into the more visible areas above this site.

SCHWEDEL

Mahrer, P. R., Evans, J. A., and Steinberg, I.: Scleroderma: Relation of Pulmonary Changes to Esophageal Disease. Ann. Int. Med. **40:** 92, (Jan.), 1954.

Scleroderma is a systemic disease involving the collagenous tissue. The skin, gastrointestinal tract including the esophagus, and the cardiovascular, musculoskeletal, genitourinary and pulmonary systems may be involved. Dysphagia is a common complaint with esophageal involvement. Because of the association of aspiration pneumonitis and fibrosis with the dysphagia of cardiospasm, the authors undertook the present survey in order to examine the possibility that the pulmonary changes in scleroderma are secondary to aspiration. If aspiration were the chief cause of the pulmonary changes in scleroderma, esophageal lesions would be present in all cases with pulmonary findings.

In the authors' cases, 69 per cent had esophageal involvement. Unlike the pulmonary fibrosis seen in cardiospasm, the lung lesions in scleroderma in one-half of the cases showed characteristic cystic changes. Thus, while aspiration pneumonia and subsequent pulmonary fibrosis may conceivably occur, they are not the primary factors in the pulmonary disease.

DENNISON

Radner, S.: Suprasternal Puncture of the Left Atrium for Flow Studies. Acta med. scandinav. **148:** 57 (Fasc. 1), 1954.

A new technic of direct puncture of the left atrium was applied in five cases. The puncture was made with a special needle from the suprasternal fossa through the space between the trachea and the aortic arch. No complications were encountered.

AUTHOR

Bachman, K. P., Foster, C. G., Jackson, M. A., Shershin, P. H., and Oard, H. C.: Radioactive Gold Instilled Intrapericardially: Report of a Case. Ann. Int. Med. **40:** 698 (Apr.), 1954.

An instance is reported of intrapericardial instillation of radioactive colloidal gold (Au^{198}) in the treatment of massive, recurring serosanguineous pericardial effusion arising from pericardial and myocardial metastases of duct infiltrating mammary carcinoma. Radioactive gold intrapericardially resulted in a temporary decrease of the pericardial effusion and alleviation of symptoms, and produced a definite radiation effect upon the tumor tissue without significant injury to normal tissues.

WENDKOS

Ferrer, M. I., and Harvey, R. M.: The Etiology of Secondary Pulmonary Hypertension. Bull. New York Acad. Med. **30:** 195 (Mar.), 1954.

The authors consider the subject of pulmonary hypertension by discussing the various mechanisms that are able to produce an elevation of the pulmonary arterial pressure in congenital and acquired heart disease. In congenital heart disease pulmonary hypertension usually arises from an increased flow of blood into the pulmonary circuit owing to left-to-right shunts. This alteration of the pulmonary circulation in patients with interatrial septal defect or patent ductus arteriosus may result, however, in a loud pulmonic second sound, a large pulmonary artery, and right ventricular hypertrophy in the absence of an elevated pulmonary pressure. The diagnosis of pulmonary hypertension in such cases, therefore, should not be made solely on these findings. These cases indicate that an increased pulmonary blood flow in an otherwise normal pulmonary vascular tree can be tolerated without producing pulmonary hypertension. In acquired heart disease, pulmonary hypertension may be due to failure of the left ventricle without concomitant failure of the right ventricle. In chronic cor pulmonale, pulmonary hypertension may result from anoxia due to pulmonary disease, such as emphysema, or anatomic alterations of the pulmonary vascular bed, such as fibrosis or multiple pulmonary emboli. If the anoxia can be relieved, circulatory compensation may be restored. With fibrosis or emboli, however, the pulmonary hypertension may be irreversible and the prognosis in such cases is poor. Pulmonary hypertension in mitral stenosis may arise from mechanical block of the stenosed valve, sclerotic pulmonary vascular lesions complicating mitral stenosis, and failure of the left ventricle. The first factor may be remedied by surgery and the latter by digitalization. The pulmonary vascular changes may not be irreversible and may improve after a period of time, if the other factors are corrected. The diagnosis of primary pulmonary hypertension can be made only when all the etiologic factors discussed above can be excluded

SAGALL

Dresdale, D. T., Michtom, R. J., and Schulz, M.: Recent Studies in Primary Pulmonary Hypertension Including Pharmacodynamic Observations on Pulmonary Vascular Resistance. Bull. New York Acad. Med. **30:** 195 (Mar.), 1954.

Primary pulmonary hypertension is distinguished from secondary pulmonary hypertension by the absence of intrinsic heart or lung disease and by the absence of mechanical obstruction in the pulmonary circulation. The syndrome of primary pulmonary hypertension is distinctive and shows definite clinical characteristics. All cases show marked right ventricular hypertrophy. Pulmonary vascular sclerosis is not necessarily part of the syndrome. When present, the vascular changes are found proximal to the capillaries and consist mainly of atheromatous lesions of the stem and large elastic arteries. The smaller arteries may also be obliterated by fibrous intimal thickening. Although the majority of patients with this condition are between 20 and 40 years old, it has been found in all age groups. The course of the disease is malignant, with right heart failure frequently terminating in sudden death. The prominent clinical features are exertional dyspnea and weakness, substernal and left chest pain simulating angina pectoris, and exertional syncope. Palpitation, orthopnea, and hemoptysis are encountered less frequently. The physical findings consist of distention of the neck veins, hepatomegaly, right ventricular hypertrophy, accentuation of the second pulmonary sound, systolic murmurs resulting from relative tricuspid insufficiency and pulmonary artery dilatation, and diastolic murmurs due to a functional pulmonary valvular insufficiency. Cyanosis and clubbing of the fingers usually appear late in the course of disease. Routine laboratory tests are usually normal except for occasional mild polycythemia. Pulmonary function studies are within normal limits. Right heart catheterization reveals marked elevation of the pulmonary artery pressure, normal systemic artery pressure, low cardiac output, increased arteriovenous oxygen difference, elevated right ventricular end-diastolic pressure and normal arterial oxygen saturation. The characteristic x-ray findings consist of right ventricular hypertrophy, bulging pulmonary artery, prominent hilar vessels and normal or decreased intrapulmonary vascular markings.

The authors present evidence to show that Priscoline, administered intravenously, exerts a beneficial effect in this syndrome by reducing the pulmonary vascular resistance resulting in a decrease in the pulmonary arterial pressure. Tetraethylammonium chloride, a ganglionic blocking agent, was not as effective. Similar modification of the pulmonary vascular resistance by Priscoline was found in normal patients with pulmonary hypertension induced by anoxia and in pulmonary hypertension secondary to pulmonary disease. Priscoline was also demonstrated to neutralize a right-to-left interatrial shunt in a patient with primary pulmonary hypertension and patent foramen ovale.

SAGALL

BOOK REVIEWS

The Uncommon Heart Diseases. *Nathaniel E. Reich, M.D.* Springfield, Ill., Charles C Thomas, 1954. 516 pages, 110 figures. $10.50.

For a long time there has been need for an encyclopedia of rare or uncommon heart diseases as a supplement to standard reference works on the heart. The purpose of Reich's new volume is to supply this need. Ideally such a book should be complete, comprehensive, and up-to-date. It should be a repository for references to all the classic works on rare and unusual heart disease. Although this textbook makes a good healthy step in this direction, it falls far short of completely satisfying the requirements.

The book is well organized, excellently printed and has a satisfactory index, a most important feature of a book on rare diseases. The numerous illustrations are excellently reproduced. The title of the book is misleading or inadequate when one considers that such a large amount of space is given over to the effects of drugs, electrolytes and toxins on the cardiovascular system. The references are good but are in no sense complete. One looks in vain for mention of Kissane's classic work on trauma. There is little or no discussion of the effect of exercise and strain on rupture of the aortic valve. Although Rich and Gregory's work is quoted numerous times, Zeek's opposite views of the pathogenesis of arteritis are not mentioned. Dissecting aneurysm is not included. There is no discussion of hereditary hemorrhagic telangiectasia and its association with pulmonary arteriovenous aneurysm, and no discussion of idiopathic hypertrophy of the heart. The generally accepted explanation for the increased x-ray shadows of the heart in myxedema, namely pericardial effusion, is barely mentioned and the outmoded concept of myxedema heart is set forth in detail. There is no mention of stilbamidine in treatment of blastomycosis and no discussion of parietal endocardial thrombosis with cardiovascular collagenosis or fibroelastosis. The feasibility of making a diagnosis of myxoma of the left auricle which acts as a ball valve thrombosis is not mentioned, nor are signs of ball valve thrombosis discussed. Curiously there is no mention of the early classic work of Soma Weiss or Von Bonsdorff, who gathered together systematically for the first time in readily available form a collection of rare diseases affecting the heart.

The first chapter, on nonstructural cardiovascular abnormalities, takes up pathophysiology and departs in no way from the standard text in this respect. Indeed the effects of exercise, anoxia, digestive system disorders, hemorrhage, anesthesia, operations, and pregnancy hardly come in the range of uncommon cardiovascular anomalies. Certainly in future editions this could be left out and some of the rare cardiac diseases not included could be put in.

There are occasional lapses in style, fortunately very rare, which stand out in an otherwise very readable book: for instance, on page 28, with reference to myocardial infarction, it is stated, "acute episodes should be allowed to heal"; there is also the statement that myocardial involvement is the "most lethal" complication of diphtheria, and "data" is used as a singular noun. In general the writing is smooth. It is to be hoped that the accuracy of the bibliographic references is not reflected in the spelling of some of the authors' names, seven errors being detected in a casual reading. At times, authors mentioned in the text are not noted in the references.

The space taken by these minor criticisms should not indicate that this is a poor book. It is excellent and the defects can be corrected readily. It meets a long-felt want. Its great virtue is that it brings together in small compass and in a handy fashion good discussion and a source of scattered and miscellaneous references to innumerable out-of-the-way diseases and disorders. The author's industry and experience are reflected in the scope of the topics covered. Almost any practising internist and certainly all cardiologists will be glad to have available a reference work to which they can go for discussion of rare and unusual diseases. It is hoped that future editions will include some of the rare diseases which have been omitted and that an effort will be made to make the references more complete so that this volume will indeed be an encyclopedia. It is a very excellent start in the right direction, and its full benefit will be realized by a few additions and corrections.

WILLIAM B. BEAN

Sympathetic Control of Human Blood Vessels. *H. Barcroft, M.D., and H. J. C. Swan, Ph.D.* London, Edward Arnold; Baltimore, Williams & Wilkins, 1953. Monographs of Physiological Society, No. I. 165 pages, 77 Figures, 9 Tables. $3.75.

The authors have drawn upon a rich background of research and experience to compile this small volume which contains material of interest to students, clinicians and investigators.

The material presented is based mainly on studies of the circulation in the extremities and, as stated in the foreword to the book, is not intended to serve as a review of the subject. Certain fundamental experiments are described in detail and the reader is carried in a simple stepwise manner through the circulation in skeletal muscle as influenced by sym-

pathetic vasoconstrictor and vasodilator nerves, adrenaline and noradrenaline, exercise and sympathetic deneveration. The action of sympathomimetic drugs on the circulation is discussed briefly. The chapter devoted to adrenergic blockade is unfortunately rather incomplete. The value of the book would have been enhanced greatly if more attention had been directed to this subject which has received much study in recent years. The discussion of the vasovagal syndrome is exceptionally well written and quite comprehensive. Beginners in the field will find the appendix quite valuable as it contains an excellent description of the historical background and methods of plethysmography.

The book contains a number of well-chosen illustrations and references and is well indexed.

GUS CASTEN

Acute Pulmonary Edema. Modern Medical Monograph, No. 10. *Mark D. Altschule.* New York, Grune and Stratton, 1954. 78 pages. $3.50.

As stated in the author's introduction, the purpose of this book is to relate the manifestations and treatment of acute pulmonary edema to certain physiologic phenomena. This book is divided into four sections. In the section on clinical manifestations, symptoms and signs of acute pulmonary edema are described in five phases: onset, interstitial phase, intra-alveolar phase, shock and terminal phase. The intra-alveolar phase may be followed by remission or by shock. Acute pulmonary edema in relation to angina pectoris and chronic cardiac decompensation is discussed. Differential diagnosis between bronchial asthma and cardiac asthma is also considered.

The section on basic physiology is begun with a review of the changes in etiologic concepts of acute pulmonary edema. There are strong objections to the unitary theory of left ventricular failure in all cases. The pulmonary fluid dynamics are discussed and the methods of producing experimental pulmonary edema briefly described. According to the author the fundamental disorder leading to acute pulmonary edema is excessive pulmonary capillary transudation over pulmonary lymphatic reabsorption. The important factors contributing to the imbalance are those which increase capillary transudation, those which decrease lymphatic reabsorption, and those which augment total extracellular fluid volume. Other factors such as pulmonary vasomotor changes, neurogenic reflexes and systemic arterial hypertension may also be important.

In the section on pathologic physiology the author discusses the mechanisms of dyspnea, nocturnal attacks, shock, wheezing and spontaneous remissions seen in acute pulmonary edema. Its occurrence and pathogenesis in a comprehensive list of disorders are described.

The last section concerns the treatment of acute pulmonary edema. Morphine and oxygen are highly effective in most cases but should be cautiously used in patients with chronic pulmonary disease. Aminophylline injected slowly by intravenous route is usually beneficial. Antifoaming and sympatholytic agents seem to be effective in some cases and may be more widely used in the future. The use of tourniquets, venesection, positive pressure and spinal anesthesia may be beneficial in some cases but should not be used when shock is also present. Digitalis is helpful only in those cases due primarily to heart failure, but its chief use is to prevent recurrent attacks of acute pulmonary edema. Mercurial diuretics and salt-depleting procedures may be valuable for similar reasons. The administration of veratrum derivatives may be effective in ameliorating acute pulmonary edema associated with hypertensive crises. Extrarenal dialysis may relieve pulmonary edema associated with uremic acidosis.

Several minor printing errors should be corrected in future editions. On page 15 the reference number 92 should be 93, and on page 44 the reference number 9 should be 17. There is no mention in the text of the following references: 10, 14, 15, 44 and 79. The reviewer wonders whether on page 20 the statement "inflating balloons in the *right* auricle" should not refer to the *left* auricle.

On the whole the book is well written. The presentation is clear and concise; the contents cover all the important physiologic and clinical observations. The author should be congratulated for having presented a coherent picture of the clinical and physiologic aspects of acute pulmonary edema. This monograph is recommended highly not only to the cardiologist but to all physicians interested in this problem.

PAUL N. YU

A Primer of Cardiology, ed. 2. *George E. Burch, M.D., F.A.C.P.*, Philadelphia, Lea & Febiger, 1953. 339 pages, 214 figures, 19 tables. $5.50.

In the second edition of *A Primer of Cardiology* Dr. Burch has discussed more completely than in the first edition congenital heart disease, the treatment of congestive heart failure, coronary artery disease, the treatment of syphilitic heart disease and the abnormal physiology of congestive heart failure. Illustrations in the first edition have been improved in the second edition, and a number of new illustrations added. The author has been extremely successful in presenting in a fascinating manner the fundamental physiology of the heart and circulation and the pathologic physiology responsible for the abnormal symptoms and signs of heart disease.

The book is divided into five chapters. Chapter I deals with applied cardiac anatomy. Chapter II

deals with the classifications of heart disease, the signs and symptoms and diagnosis of heart disease, a clear and stimulating review of the controversial theories concerning the mechanism of congestive heart failure, and a splendid summary of the mechanism of edema. Chapter III describes the history and physical examination in heart disease with particular reference to the genesis of murmurs, gallop rhythm, and extracardiac sounds. Chapter IV is concerned with the etiologic types of heart disease. This excellent section would be strengthened by a discussion of cor pulmonale. Chapter V is concerned with the bedside diagnosis of cardiac irregularities and is an outstanding discussion of this subject.

This reviewer is in disagreement with certain minor clinical opinions expressed by the author in this excellent book:

1. In the section on acute bacterial endocarditis (page 170) Dr. Burch has stated, "Early and adequate treatment has made the course relatively mild and the mortality rate now closely approaches zero." In our experience and in that of others acute bacterial endocarditis due to certain strains of staphylococci and other organisms resistant to antibiotics continues to have a high mortality.

2. The clinical picture of Pick's Disease (mediastinopericarditis with pseudocirrhosis of the liver), in our experience, has been regularly due to chronic constrictive pericarditis, per se, and *not* as described by Burch to adhesions constricting the inferior vena cava and hepatic veins as they enter the vena cava (page 182).

3. The author (page 173) has stated, "The etiologic incidence of pericarditis varies, about 70 per cent being pyogenic, 3 per cent tuberculous, and the remaining 27 per cent of various types." In the majority of studies of the etiology of pericarditis recently reported, pyogenic pericarditis has become rare, acute nonspecific pericarditis and tuberculous pericarditis being the etiologic agents most frequently responsible.

4. The author (page 183) has stated, "Stab wounds with hemorrhage must be sutured." In the majority of clinics pericardial paracentesis is carried out in the treatment of bloody tamponade from stab wounds and surgical suture resorted to only if the hemorrhage reoccurs.

In summary, this vigorous, original and stimulating monograph is to be highly recommended to physicians interested in heart disease as well as to medical students.

JOHNSON MCGUIRE

Autopsy Diagnosis of Congenitally Malformed Hearts. *Maurice Lev, M.D.* Springfield, Ill., Charles C Thomas, 1953. 194 pages, 115 figures. $7.50.

This monograph was written with the purpose of supplying a guide to the morphology of congenital heart disease for the autopsy surgeon. The author is well qualified to undertake such a job since he is a pathologist who has made important contributions to the morphology and embryology of congenital heart disease.

The book is divided in three parts: a short chapter (10 pages) on the examination of the congenitally abnormal heart; a 60-page section devoted to the gross morphology of the individual abnormalities found in the cardiovascular system; and an 85-page section on "pathologic complexes," which presents the various congenital syndromes and discusses briefly the embryologic background and the physiologic effects of these defects. At the end one finds a 20-page bibliography which lists monographs and well-selected articles on congenital heart disease.

The concise, well-written text, illustrated with many photographs and diagrams, makes easy reading even for one who is not well versed in the complicated subjects of cardiac malformations. The value of the monograph as a reference book in gross cardiac pathology might have been enhanced, however, if certain numerical values were included. One misses, for instance, measurements expressing the range of the various defects, and the degrees of stenosis of orifices. Furthermore, a separation of the defects which are incompatible with long survival and are only seen in infants from those found frequently in the adult heart would have been useful. Finally, rough estimates as to the frequency of the various defects have not been included.

As already mentioned, the third section of the monograph is reinforced by embryologic and physiologic comments. The embryology is very well presented. "Physiologic", or rather hemodynamic relationships are less well presented and occasionally hard to follow. For example the author states in the discussion of the large ventricular septal defect: "The left ventricle contracts against systemic and indirectly (through the defect) against pulmonary resistance, hence its thinner wall than usual." In the reviewer's opinion the inadequate explanation of the influence of hemodynamics upon morphology represents the only major weakness of this book. Dynamic alterations of blood flow resulting from congenital malformations provide the third dimension of descriptive anatomy of the malformed heart. One is fully justified, in the newborn heart, in talking in terms of hypoplasia of some sections of the cardiovascular system, even though it may be the result of an alteration of fetal blood flow. However, in the heart of the older child or the adult the growth of the cardiac ventricles or great vessels is probably affected primarily by pressure-flow relationships rather than by the way they were formed in utero. Thus, for example, a hypoplastic aorta in the Eisenmenger complex need not represent a "malformation"; and the division of the syndrome of ductus

arteriosus into two types, left ventricular type and right ventricular type, is not justified unless it is explained that the latter is the result of co-existing pulmonary hypertension.

These few criticisms are not meant to detract from the value of this exceedingly useful monograph but rather represent comment which might be used for its enlargement in a future edition. The book is recommended not only for pathologists but for clinicians dealing with congenital heart disease as well.

A. SELZER

A Bibliography of the World Literature on Blood Pressure. 1920–1950. Volume I (Authors and Titles), Volume II (Author Index and Title Index), Volume III (Abstracts). *Edited by Ernest K. Koller and Jacob Katz.* Boston, Commonwealth of Massachusetts, 1952. $5.00 for the set.

These 3 volumes together form an ambitious attempt to index the voluminous literature on hypertension published between 1920 and 1950. Volumes I and II include references to 16,460 scientific papers. In volume III are abstracts of about 1500 of these.

They form a useful catalogue for one interested in clinical and experimental aspects of hypertension. The editors point out that these volumes are the outgrowth of current investigations into the epidemiology of hypertension.

WILLIAM A. JEFFERS

Diuretic Therapy. The Pharmacology of Diuretic Agents and the Clinical Management of the Edematous Patient. *Alfred Vogl, M.D.*, Baltimore, Williams & Wilkins, 1953. 248 pages, 5 figures, 5 tables. $5.00.

This book is a welcome addition and reflects the trend in medical publishing toward bringing out detailed treatises on relatively restricted subjects. This work, however, has application and utility for any conscientious physician, general practitioner or specialist, who has a concern to provide the very best therapeutic approach to the patient with pathologic deviations of water and electrolyte metabolism.

The text is appropriately divided into sections, the first defining and classifying edema, and outlining its pathogenesis and general principles of treatment. The second discusses indications for diuretic therapy in terms of specific disease states. The third section is a detailed outline of the diuretic drugs available, their pharmacodynamic and relative efficiency. Next the matter of antidiuretic agents is presented which seems very useful and little emphasized in other writings on the subject. Lastly there are 123 pages devoted to the clinical application of diuretic therapy, including other than diuretic agents themselves. This seems especially important to this reviewer, for failure of diuretic drugs may frequently be attributed to lack of a pathophysiologic approach to the total problem of inducing diuresis. The complications and contraindications of diuretic agents is well presented and emphasized. The bulk of the book is devoted to the problems of congestive failure of the circulation.

Dr. Vogl wisely and repeatedly points out that diuretic therapy is only symptomatic and does not cure the underlying pathophysiologic state leading to edema. Edema is only the most recent phenomenon in a long series of events.

The use of older, little used but effective diuretic agents, such as urea and Decholin, is presented appropriately and their more frequent employment is suggested. The principle that treatment should be aimed at the total patient and not just his edema is stressed. Simply the existence of edema does not necessarily indicate diuretic therapy. Furthermore diuretic therapy does not always mean the use of diuretic drugs.

It would seem useful to include in the text an explanation, perhaps by means of diagrams, an integrated concept of the terms forward and backward failure and high and low output failure of the circulation. The current trend in both investigative and clinical fields is to pull together these theories into a unified concept which has far greater bedside usability in diagnosis and therapy. The adherence to one or another theory has been a source of confusion and a block to proper interpretation of symptoms and signs in clinical medicine.

The book occasionally leaves something to be desired from the point of view of the medical student. There is the implication that alkalosis develops because of loss of chloride and rise in serum bicarbonate. The excessive excretion of hydrogen ion is the reason for the development of alkalosis of body fluids. This is a minor criticism that constitutes a plea for closer correlation of terminology between preclinical and clinical teachers. The term "hydrogen ion control" is a more adequate expression than acid-base balance and other such terms. The student is entitled to a certain amount of sympathy when he is told by clinical teachers that he measures the serum concentration of carbon dioxide, a volatile acid, and obtains the measurement of fixed base. Also it seems preferable to use the term "sodium" rather than "salt" in order to emphasize the importance of sodium in maintaining extracellular fluid volume. The use of the term sodium will also remind us that the electrolyte lost or retained is not sodium chloride but a mixture of chloride, bicarbonate and other anions along with sodium and potassium. The biochemical and physiologic concepts of excretion of sodium, chloride and hydrogen ion as elucidated by Robert Pitts with his diagrams correlated with the effect of organic mercurials would seem to have real usefulness and enhance the value of the text from an academic point of view.

The chapter on antidiuretic agents seems es-

deals with the classifications of heart disease, the signs and symptoms and diagnosis of heart disease, a clear and stimulating review of the controversial theories concerning the mechanism of congestive heart failure, and a splendid summary of the mechanism of edema. Chapter III describes the history and physical examination in heart disease with particular reference to the genesis of murmurs, gallop rhythm, and extracardiac sounds. Chapter IV is concerned with the etiologic types of heart disease. This excellent section would be strengthened by a discussion of cor pulmonale. Chapter V is concerned with the bedside diagnosis of cardiac irregularities and is an outstanding discussion of this subject.

This reviewer is in disagreement with certain minor clinical opinions expressed by the author in this excellent book:

1. In the section on acute bacterial endocarditis (page 170) Dr. Burch has stated, "Early and adequate treatment has made the course relatively mild and the mortality rate now closely approaches zero." In our experience and in that of others acute bacterial endocarditis due to certain strains of staphylococci and other organisms resistant to antibiotics continues to have a high mortality.

2. The clinical picture of Pick's Disease (mediastinopericarditis with pseudocirrhosis of the liver), in our experience, has been regularly due to chronic constrictive pericarditis, per se, and *not* as described by Burch to adhesions constricting the inferior vena cava and hepatic veins as they enter the vena cava (page 182).

3. The author (page 173) has stated, "The etiologic incidence of pericarditis varies, about 70 per cent being pyogenic, 3 per cent tuberculous, and the remaining 27 per cent of various types." In the majority of studies of the etiology of pericarditis recently reported, pyogenic pericarditis has become rare, acute nonspecific pericarditis and tuberculous pericarditis being the etiologic agents most frequently responsible.

4. The author (page 183) has stated, "Stab wounds with hemorrhage must be sutured." In the majority of clinics pericardial paracentesis is carried out in the treatment of bloody tamponade from stab wounds and surgical suture resorted to only if the hemorrhage reoccurs.

In summary, this vigorous, original and stimulating monograph is to be highly recommended to physicians interested in heart disease as well as to medical students.

JOHNSON MCGUIRE

Autopsy Diagnosis of Congenitally Malformed Hearts. *Maurice Lev, M.D.* Springfield, Ill., Charles C Thomas, 1953. 194 pages, 115 figures. $7.50.

This monograph was written with the purpose of supplying a guide to the morphology of congenital heart disease for the autopsy surgeon. The author is well qualified to undertake such a job since he is a pathologist who has made important contributions to the morphology and embryology of congenital heart disease.

The book is divided in three parts: a short chapter (10 pages) on the examination of the congenitally abnormal heart; a 60-page section devoted to the gross morphology of the individual abnormalities found in the cardiovascular system; and an 85-page section on "pathologic complexes," which presents the various congenital syndromes and discusses briefly the embryologic background and the physiologic effects of these defects. At the end one finds a 20-page bibliography which lists monographs and well-selected articles on congenital heart disease.

The concise, well-written text, illustrated with many photographs and diagrams, makes easy reading even for one who is not well versed in the complicated subjects of cardiac malformations. The value of the monograph as a reference book in gross cardiac pathology might have been enhanced, however, if certain numerical values were included. One misses, for instance, measurements expressing the range of the various defects, and the degrees of stenosis of orifices. Furthermore, a separation of the defects which are incompatible with long survival and are only seen in infants from those found frequently in the adult heart would have been useful. Finally, rough estimates as to the frequency of the various defects have not been included.

As already mentioned, the third section of the monograph is reinforced by embryologic and physiologic comments. The embryology is very well presented. "Physiologic", or rather hemodynamic relationships are less well presented and occasionally hard to follow. For example the author states in the discussion of the large ventricular septal defect: "The left ventricle contracts against systemic and indirectly (through the defect) against pulmonary resistance, hence its thinner wall than usual." In the reviewer's opinion the inadequate explanation of the influence of hemodynamics upon morphology represents the only major weakness of this book. Dynamic alterations of blood flow resulting from congenital malformations provide the third dimension of descriptive anatomy of the malformed heart. One is fully justified, in the newborn heart, in talking in terms of hypoplasia of some sections of the cardiovascular system, even though it may be the result of an alteration of fetal blood flow. However, in the heart of the older child or the adult the growth of the cardiac ventricles or great vessels is probably affected primarily by pressure-flow relationships rather than by the way they were formed in utero. Thus, for example, a hypoplastic aorta in the Eisenmenger complex need not represent a "malformation"; and the division of the syndrome of ductus

arteriosus into two types, left ventricular type and right ventricular type, is not justified unless it is explained that the latter is the result of co-existing pulmonary hypertension.

These few criticisms are not meant to detract from the value of this exceedingly useful monograph but rather represent comment which might be used for its enlargement in a future edition. The book is recommended not only for pathologists but for clinicians dealing with congenital heart disease as well.

A. SELZER

A Bibliography of the World Literature on Blood Pressure. 1920–1950. Volume I (Authors and Titles), Volume II (Author Index and Title Index), Volume III (Abstracts). *Edited by Ernest K. Koller and Jacob Katz.* Boston, Commonwealth of Massachusetts, 1952. $5.00 for the set.

These 3 volumes together form an ambitious attempt to index the voluminous literature on hypertension published between 1920 and 1950. Volumes I and II include references to 16,460 scientific papers. In volume III are abstracts of about 1500 of these.

They form a useful catalogue for one interested in clinical and experimental aspects of hypertension. The editors point out that these volumes are the outgrowth of current investigations into the epidemiology of hypertension.

WILLIAM A. JEFFERS

Diuretic Therapy. The Pharmacology of Diuretic Agents and the Clinical Management of the Edematous Patient. *Alfred Vogl, M.D.*, Baltimore, Williams & Wilkins, 1953. 248 pages, 5 figures, 5 tables. $5.00.

This book is a welcome addition and reflects the trend in medical publishing toward bringing out detailed treatises on relatively restricted subjects. This work, however, has application and utility for any conscientious physician, general practitioner or specialist, who has a concern to provide the very best therapeutic approach to the patient with pathologic deviations of water and electrolyte metabolism.

The text is appropriately divided into sections, the first defining and classifying edema, and outlining its pathogenesis and general principles of treatment. The second discusses indications for diuretic therapy in terms of specific disease states. The third section is a detailed outline of the diuretic drugs available, their pharmacodynamic and relative efficiency. Next the matter of antidiuretic agents is presented which seems very useful and little emphasized in other writings on the subject. Lastly there are 123 pages devoted to the clinical application of diuretic therapy, including other than diuretic agents themselves. This seems especially important to this reviewer, for failure of diuretic drugs may frequently be attributed to lack of a pathophysiologic approach to the total problem of inducing diuresis. The complications and contraindications of diuretic agents is well presented and emphasized. The bulk of the book is devoted to the problems of congestive failure of the circulation.

Dr. Vogl wisely and repeatedly points out that diuretic therapy is only symptomatic and does not cure the underlying pathophysiologic state leading to edema. Edema is only the most recent phenomenon in a long series of events.

The use of older, little used but effective diuretic agents, such as urea and Decholin, is presented appropriately and their more frequent employment is suggested. The principle that treatment should be aimed at the total patient and not just his edema is stressed. Simply the existence of edema does not necessarily indicate diuretic therapy. Furthermore diuretic therapy does not always mean the use of diuretic drugs.

It would seem useful to include in the text an explanation, perhaps by means of diagrams, an integrated concept of the terms forward and backward failure and high and low output failure of the circulation. The current trend in both investigative and clinical fields is to pull together these theories into a unified concept which has far greater bedside usability in diagnosis and therapy. The adherence to one or another theory has been a source of confusion and a block to proper interpretation of symptoms and signs in clinical medicine.

The book occasionally leaves something to be desired from the point of view of the medical student. There is the implication that alkalosis develops because of loss of chloride and rise in serum bicarbonate. The excessive excretion of hydrogen ion is the reason for the development of alkalosis of body fluids. This is a minor criticism that constitutes a plea for closer correlation of terminology between preclinical and clinical teachers. The term "hydrogen ion control" is a more adequate expression than acid-base balance and other such terms. The student is entitled to a certain amount of sympathy when he is told by clinical teachers that he measures the serum concentration of carbon dioxide, a volatile acid, and obtains the measurement of fixed base. Also it seems preferable to use the term "sodium" rather than "salt" in order to emphasize the importance of sodium in maintaining extracellular fluid volume. The use of the term sodium will also remind us that the electrolyte lost or retained is not sodium chloride but a mixture of chloride, bicarbonate and other anions along with sodium and potassium. The biochemical and physiologic concepts of excretion of sodium, chloride and hydrogen ion as elucidated by Robert Pitts with his diagrams correlated with the effect of organic mercurials would seem to have real usefulness and enhance the value of the text from an academic point of view.

The chapter on antidiuretic agents seems es-

pecially appropriate and little appreciated. For instance, the frequency with which the edematous patient receives narcotics or barbiturates along with mercurial diuretics would seem more than occasionally to play a role in compromising a satisfactory diuresis.

The value of rest in diuretic therapy as well as the more recent investigative data on the effect of passive erect posture on diuresis, renal plasma flow and glomerular filtration rate are brought out. It is unfortunate that the book was published without a discussion of the recent carbonic anhydrase blocking agent, Diamox. Dr. Vogl's pathophysiologic approach to diuretic therapy might alter the present unbridled enthusiasm for its use. This will certainly constitute an addition to a revision.

As Dr. Fishberg points out in the foreword, "A work on diuretic therapy by the physician who first observed the remarkable diuretic properties of the organic mercurials is, of course, an event." The book constitutes the best available source for the details of basic physiology, pharmacology and clinical application of diuretic therapy.

JOHN H. BLAND

A Primer of Congestive Heart Failure. *George E. Burch, M.D.* Publication No. 190, American Lecture Series. A Monograph in American Lectures in Internal Medicine, edited by Roscoe L. Pullen, M.D. Springfield, Ill. Charles C Thomas, 1954. 126 pages, 15 figures, 1 table. $4.00.

The title of this excellent book belies the comprehensive nature of the subject matter. The book is divided into sections dealing with the mechanism of congestive heart failure, treatment of congestive heart failure, digitalis, and mercurial diuretics. Each section has a useful and selective bibliography. The current concepts of congestive failure are reviewed in a well-organized and lucid manner. The discussions are enhanced by the use of effective diagrams. The gaps in our knowledge and the inconsistencies of the theories of both forward and backward failure are pointed up in an authoritative and critical manner.

The management of the patient with congestive heart failure is discussed in detail, including rest, nursing care, diet, oxygen, drugs and their dosage. The indications, methods of administration, modes of action and toxicity of digitalis and mercurial diuretics are covered in a thorough manner. One might take exception to several statements, such as the recommendation to use oxygen and penicillin in every patient with congestive heart failure and the statement, "most patients with chronic congestive heart failure do not need mercurial diuretics." On the whole, the book is a valuable addition and it is highly recommended for students, practitioners, and internists.

R. B. LOGUE

Clinical Unipolar Electrocardiography, ed. 2. *Bernard S. Lipman A.B., M.D., and Edward Massie, A.B., M.D.* Chicago, Year Book Publishers, 1953. 309 pages, 260 figures. $6.50.

This book presents a simple, brief and practical introduction to clinical unipolar electrocardiography. It covers the subject material in an acceptable and useful way, similar to several other introductory texts in the same field. The brief presentation is generally satisfactory at an elementary level of consideration but is necessarily inadequate on many smaller points for a thorough understanding. The subject matter covers a somewhat standardized discussion of unipolar technic, polarization and repolarization and the effects of position, ventricular enlargement, bundle-branch block and myocardial damage, ischemia, injury and infarction.

The chief distinguishing feature of this text is a small blocked diagrammatic representation of a QRS-T pattern every time such a pattern is mentioned in the text. This device increases the space requirement in printing, but this pictorial representation placed directly in the sequency of the text is a most valuable aid in simplifying and accelerating one's grasp of the material.

Two new sections have been added in this second edition. They are a brief discussion of cardiac arrhythmias and a group of illustrative electrocardiograms; the latter is particularly valuable, filling the gap left by the diagrammatic presentations.

Perhaps the major deficiency in this book is the limited approach of unipolar electrocardiography with avoidance of the concepts of vectorcardiography. By this time, such an explanation of electrocardiography, though simple and readily grasped, is incomplete and perhaps somewhat misleading. It is the feeling of the reviewer that even an introductory text of this nature should present the orientation and basic concepts of vectorcardiography, with a consideration of the electrocardiogram as a representation of sum totals of instantaneous electric forces from moment to moment.

PAUL M. ZOLL

NEOHYDRIN®

BRAND OF CHLORMERODRIN

NORMAL OUTPUT OF SODIUM AND WATER

Individualized daily dosage of NEOHYDRIN -- 1 to 6 tablets a day as needed -- prevents the recurrent daily sodium and water reaccumulation which may occur with single-dose diuretics. Arbitrary limitation of dosage or rest periods to forestall refractivity are unnecessary. Therapy with NEOHYDRIN need never be interrupted or delayed for therapeutic reasons. Because it curbs sodium retention by inhibiting succinic dehydrogenase in the kidney only, NEOHYDRIN does not cause side actions due to widespread enzyme inhibition in other organs.

Prescribe NEOHYDRIN in bottles of 50 tablets. There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.

Leadership in diuretic research

LAKESIDE LABORATORIES, INC. · MILWAUKEE 1, WISCONSIN

Circulation

DECEMBER 1954
VOL. X NO. 6

A JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS

INDEX ISSUE

PATHOLOGY OF THE PULMONARY VASCULAR TREE. IV. STRUCTURAL CHANGES IN THE PULMONARY VESSELS IN CHRONIC LEFT VENTRICULAR FAILURE
Roger C. Smith, Howard B. Burchell, and Jesse E. Edwards 801

TREATMENT OF ANGINA PECTORIS WITH CINCHONA ALKALOIDS
Joseph E. F. Riseman, Lester A. Steinberg, and George E. Altman 809

TRAUMATIC AORTIC ANEURYSMS
Edwin M. Goyette, Hu A. Blake, James H. Forsee, and Henry Swan 824

"ISOLATED" T-WAVE NEGATIVITY IN THE "ISCHEMIC PHASE" OF MYOCARDIAL INFARCTION IN MAN. *Robert C. Schlant, Harold D. Levine, and C. Cabell Bailey* 829

THE MISINTERPRETATION OF ELECTROCARDIOGRAMS WITH POSTPRANDIAL T-WAVE INVERSION. *Isidore Rochlin and W. L. Jack Edwards* 843

REPEAT VARIABILITY OF SPATIAL QRS AND T VECTORS
Ernst Simonson and Ancel Keys 850

ELECTROCARDIOGRAPHIC FINDINGS IN EPIDEMIC HEMORRHAGIC FEVER
Carl M. Pearson and Robert J. Hall 855

POSTOPERATIVE CHANGES IN THE ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE. I. PURE PULMONARY STENOSIS. *Bernhard Landtman* 859

POSTOPERATIVE CHANGES IN THE ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE. II. COARCTATION OF THE AORTA AND PATENT DUCTUS ARTERIOSUS
Bernhard Landtman 871

STUDIES ON TOLERANCE TO GANGLIONIC BLOCKING AGENTS IN MAN. REVERSAL OF DEPRESSOR ACTION OF QUATERNARY AMMONIUM COMPOUNDS
A. S. Dontas and S. W. Hoobler 887

ESTROGEN INHIBITION OF CORTICOID HYPERTENSION IN CHICKENS. *J. Stamler* 896

THE EFFECT OF CONGESTIVE HEART FAILURE ON BLOOD VOLUME AS DETERMINED BY RADIOCHROMIUM-TAGGED RED CELLS. *Seymour Eisenberg* 902

THE EFFECT OF ACUTE SALT LOADS ON THE URINARY SODIUM OUTPUT OF NORMOTENSIVE AND HYPERTENSIVE PATIENTS BEFORE AND AFTER SURGERY
Jesse E. Thompson, Thomas F. Silva, Dera Kinsey, and Reginald H. Smithwick 912

CLINICAL PROGRESS. ERRORS IN THE RECOGNITION AND TREATMENT OF HEART DISEASE. *R. Bruce Logue and J. Willis Hurst* 920

ABSTRACTS 933

BOOK REVIEWS 956